FORMULATION AND EVALUATION OF METOPROLOL SUCCINATE EXTENDED RELEASE TABLETS

Dissertation submitted to

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY, CHENNAI.

In partial fulfilment of the requirement for the

Award of the degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

By

Reg. No: 261510404

Under the guidance of

Dr. J.JEYAANANTHI, M.Pharm., Ph.D.,

ARULMIGU KALASALINGAM COLLEGE OF PHARMACY,

ANAND NAGAR, KRISHNANKOIL-626126,

TAMILNADU.

OCTOBER 2017

Dr. N.VENKATESHAN, M.Pharm., Ph.D.,
Principal,
Arulmigu Kalasalingam College of Pharmacy,
Anand nagar, Krishnankoil.

CERTIFICATE

This is to certify that the dissertation entitled, **"FORMULATION AND EVALUATION OF METOPROLOL SUCCINATE EXTENDED RELEASE TABLETS".** Submitted by **Reg. No: 261510404** was carried out in the Department of Pharmaceutics, Arulmigu Kalasalingam College of Pharmacy, Krishnankoil in partial fulfilment of the requirement for the Degree of Master of Pharmacy in Pharmaceutics, is a bonafide work carried out by him, under my guidance and supervision in the Department of Pharmaceutics, Arulmigu Kalasalingam College of Pharmacy, Krishnankoil during the academic year 2016 - 2017.

This dissertation is forwarded to the controller of examinations, The Tamilnadu Dr.M.G.R. Medical University, Chennai.

Place: Krishnankoil **Dr. N.VENKATESHAN, M.Pharm., Ph.D**

Date: **Principal**

Dr. J.JEYAANANTHI, M.Pharm., Ph.D.,
Department of Pharmaceutics,
Arulmigu Kalasalingam College of Pharmacy,
Anand nagar, Krishnankoil.

CERTIFICATE

This is to certify that the work embodied in this thesis entitled, **"FORMULATION AND EVALUATION OF METOPROLOL SUCCINATE EXTENDED RELEASE TABLETS".** Submitted to the Tamilnadu Dr. M.G.R. Medical University, Chennai was carried out by **Reg. No: 261510404** in the Department of Pharmaceutics, Arulmigu Kalasalingam College of Pharmacy, Krishnankoil for the partial fulfilment for the award of degree of Master of Pharmacy in Pharmaceutics under my supervision.

This work is original and has not been submitted in part or full for any other degree or diploma of this or any other university.

Place: Krishnankoil
Date:

Dr. J.JEYAANANTHI, M.Pharm., Ph.D
Department of Pharmaceutics

EVALUATION CERTIFICATE

This is to certify that the work embodied in this thesis entitled **"Formulation and Evaluation of Metoprolol Succinate Extended Release Tablets".** Submitted to the Tamilnadu Dr. M.G.R. Medical University Chennai, was carried out by **Reg. No: 261510404** in the department of Pharmaceutics, Arulmigu Kalasalingam College of Pharmacy, Krishnankoil in the partial fulfilment of the degree of "Master of Pharmacy" in Pharmaceutics under supervision of **Dr. J.JEYAANANTHI M.Pharm., Ph.D.,** Department of Pharmaceutics, Arulmigu Kalasalingam College of Pharmacy, Krishnankoil.

This work is original and has not been submitted in part or full for the award of any other degree or diploma of any other University.

Internal Examiner **External Examiner**

Convener of Examination

DECLARATION

The work presented in this thesis entitled **"Formulation and Evaluation of Metoprolol Succinate Extended Release Tablets".** Was carried out by me in the department of Pharmaceutics, Arulmigu Kalasalingam College of Pharmacy, Krishnankoil. Under the direct supervision of **Dr. J.JEYAANANTHI M.Pharm., Ph.D.,** Department of Pharmaceutics, Arulmigu Kalasalingam College of Pharmacy, Krishnankoil.

This work is original and has not been submitted in part or full for the award of any other degree or diploma of any other University.

Place: Krishnankoil

Date:

Reg No: 261510404
M.Pharm. II Year,
Department of Pharmaceutics,
Arulmigu Kalasalingam College of
Pharmacy, Anand nagar, Krishnankoil.

Dedicated to God,
My Family ,
Teachers & Friends

ACKNOWLEDGEMENT

“You will meet more angles on a winding path than on a straight one”

Working on a research project needs guidance, support and encouragement. Getting such help is only by the grace of god.

First and foremost, I would like to thank the almighty God Jesus for giving me strength in my weakness and guiding me through all my darkness and taught the way in a difficult part of life. The completion of this project is not only fulfilment of my dream but also in fulfilment of the dream of my parents who have taken lots of pain in my making.

I hereby take this opportunity to acknowledge all those who have helped me in the completion of this dissertation work.

I would like to express our thanks to the founder of our institution **“Kalvivallal” Thiru. T.Kalasalingam, B.com** for providing us required facilities for extending a rich. And also I convey thank **“Ilaiyavallal” Dr.K.Sridharan, Ph.D.,** dynamic **directors Dr.S.Shasianand, Ph.D., Mr.S.Arjunkalasalingam, M.S.,** and management of our institution for providing us necessary infrastructure.

It is an honour to pay my respect and heartfelt thanks to our most respected principal **Dr.N.Venkateshan, M.Pharm, Ph.D.,** who gave me the opportunity to do this project in Industry.

I would like to express our thanks to the founder of the Caplin Point Laboratories Pvt Ltd, **Dr. S.Sridhar Ph.D., and Dr. G.Hariharan,** General Manager of Caplin Point laboratories for providing permission to utilize the facilities available in the industry for my project work.

It gives me immense pleasure to express deepest thanks, heartfelt, indebtedness and respectful Guide **Dr.J.Jeyaananthi, M.Pharm., Ph.D.,** for his encouragement and guidance during the course of the project, for providing suggestions during the project.

I express my special thanks to **Mr.M.Duraivel, M.Pharm,** for providing much of stimuli in the form of suggestions and guidance were of enormous support for me during my entire research work. He was a good mentor to answer any question regarding research.

Especially I thank, **Mr.R.Anandaraj, Mr.Easter jayaraj, Mr.K.Kaliraj, Mr.Suganesh, Mr.R.Udaiyali, Mr.G.Balamurugan** and all my friends who have willingly helped me out with their abilities for completing the project.

CONTENTS

S.No	Titles	Page.No
1	**INTRODUCTION**	1
1.1	Solid dosage forms	1
1.2	Tablets	1
1.3	Extended Release Tablets	4
1.4	Hypertension	6
2	**LITERATURE REVIEW**	8
3	**AIM AND OBJECTIVE**	20
4	**PLAN OF WORK**	21
5	**DRUG PROFILE**	22
6	**EXCIPIENT PROFILE**	25
7	**MATERIALS & METHODS**	29
7.1	Raw Material Analysis	30
7.2	Preformulation Studies	32
7.3	Formulation Development	34
7.4	Evaluation of Compressed Tablets	38
7.4.1	Description	38
7.4.2	Weight Variation	38
7.4.3	Thickness	38
7.4.4	Diameter	38
7.4.5	Friability	38
7.4.6	Tablet Disintegration Time	39
7.4.7	Assay	39
7.4.8	Uniformity of Content	39
7.4.9	*In-Vitro* Dissolution Studies	41
8	**RESULTS AND DISCUSSION**	47
9	**SUMMARY AND CONCLUSION**	58
10	**REFERENCES**	59

INTRODUCTION

1. INTRODUCTION

1.1 SOLID DOSAGE FORMS [1]

The convenient oral drug delivery has been known for decades is the most widely utilized route of administration among all the routes. It remains the preferred route of administration in the discovery and development of new drug candidates. The popularity of oral route is attributed to patient acceptance, ease of administration, accurate dosing, cost effective manufacturing methods and generally improve the shelf life of the product [1].

Oral solid forms such as tablets and capsules has been formulated and developed nowadays since they are most effective routes of administration of a new drug. Pharmaceutical products designed for oral delivery and currently available on the prescription and over the counter markets are mostly the immediate release type, which are designed for immediate release of drug for rapid absorption. Many new generations of pharmaceutical products called controlled and sustained release drug delivery system have also been developed. So the combination of both will be very much useful for immediate response and for maintaining the duration of action.

1.2 TABLETS

Tablet is defined as a compressed solid dosage form containing medicaments with or without excipients. According to the Indian Pharmacopoeia Pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing a drugs or a mixture of drugs, with or without diluents. They vary in shape and differ greatly in size and weight, depending on amount of medicinal substances and the intended mode of administration. It is the most popular dosage form and 70% of the total medicines are dispensed in the form of tablet. It was prepared by the various technique. They are wet granulation, dry granulation and direct compression as shown in fig.1.

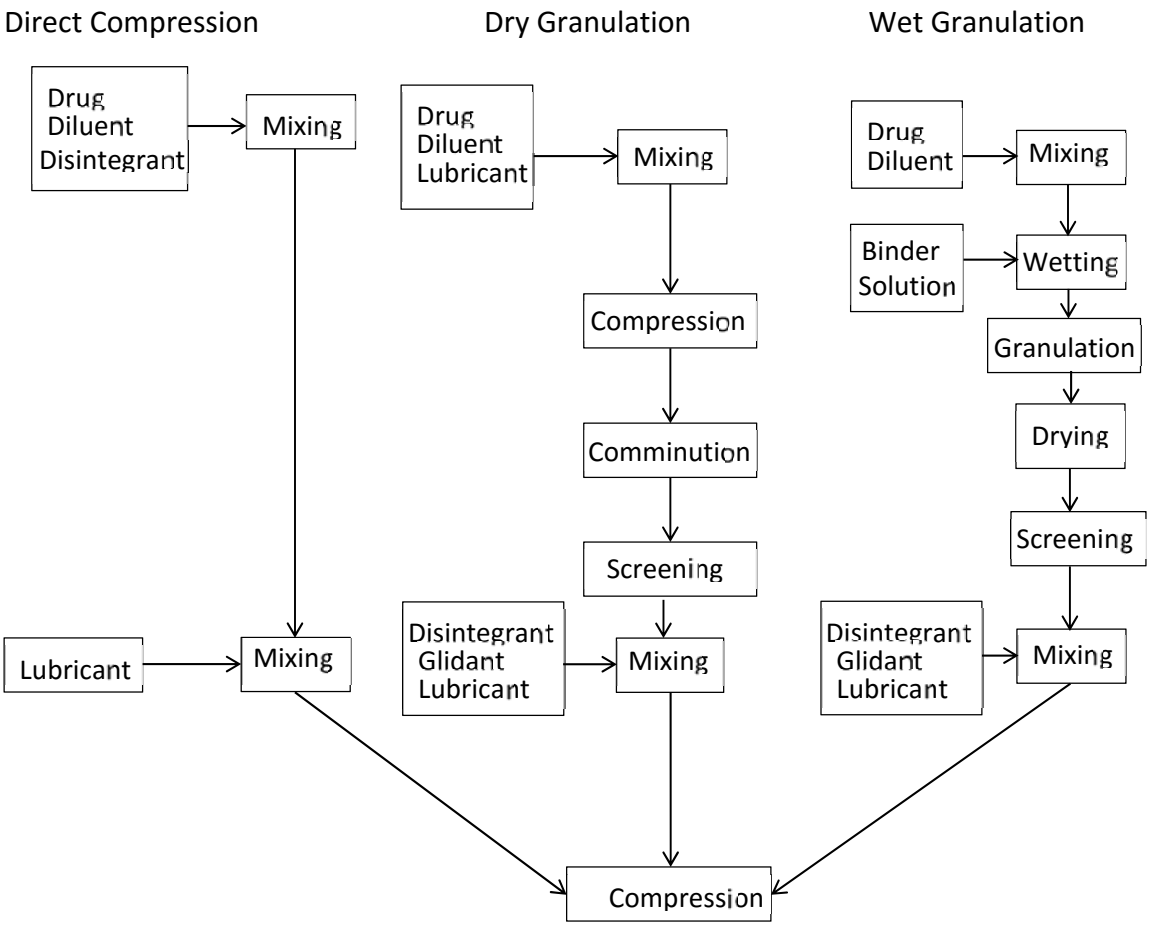


Fig.1 Various techniques of Granulation Technology on Large scale [(2)]

a) Advantages of the Tablet dosage form [(3)]:

1. They are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
2. Cost is lowest of all oral dosage form.
3. Lighter and compact.
4. Easiest and cheapest to package and strip.
5. Easy to swallowing with least tendency for hang-up.
6. Sustained release product is possible by enteric coating.
7. Objectionable odour and bitter taste can be masked by coating technique.
8. Suitable for large scale production.
9. Greatest chemical and microbial stability over all oral dosage form.
10. Product identification is easy and rapid requiring no additional steps when employing an embossed and / or monogrammed punch face.

b) Disadvantages of Tablet dosage form:

1. Difficult to swallow in case of children and unconscious patients.
2. Some drugs resist compression into dense compacts, Owing to amorphous nature, Low density character.
3. Drugs with poor wetting, Slow dissolution properties, May be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.
4. Bitter testing drugs, Drugs with an objectionable odour or drugs that are sensitive to oxygen may require encapsulation or coating.

c) Different types of Tablets [4]:

(i) Tablets ingested orally:

1. Compressed tablet
2. Multiple compressed tablets -Compression coated tablet -Layered tablet -Inlay Tablet
3. Repeat action tablet
4. Delayed release tablet
5. Sugar coated tablet
6. Film coated tablet
7. Chewable tablet
8. Targeted Tablets

(ii) Tablets used in oral cavity:

1. Buccal tablet
2. Sublingual tablet
3. Troches or lozenges
4. Dental cone

(iii) Tablets administered by other route:

1. Implantation tablet
2. Vaginal tablet

(iv) Tablets used to prepare solution:

1. Effervescent tablet
2. Dispensing tablet
3. Hypodermic tablet
4. Tablet triturates

1.3 EXTENDED RELEASE TABLETS [5]

Drug products designed to reduce the frequency of dosing by modifying the rate of drug absorption have been available for many years. Early modified-release products were often intramuscular/subcutaneous injections of suspensions of insoluble drug complexes, e.g. procaine penicillin, protamine zinc insulin, insulin zinc suspensions or injections of the drug in oil, e.g. fluphenazine decanoate. Advances in technology have resulted in novel oral modified-release dosage forms.

Many terms are used to describe modified-release products including extended-release, prolonged-release, controlled-release, controlled-delivery, slow-release and sustained-release. These preparations, by definition, have a reduced rate of release of active substance. In general, these terms are interchangeable.

Delayed-release products are modified-release, but by definition are not extended-release. They involve the release of discrete amount(s) of drug sometime after drug administration, e.g. enteric-coated products, and exhibit a lag time during which little or no absorption occurs.

While a number of such modified-release products are available as both prescription and over-the-counter drugs, only a limited number have been shown to offer a therapeutic advantage. Many of the formulations appear to have been developed to extend patents or to create a marketing advantage over conventional-release products, rather than because of clinical advantage

- Sustained blood levels
- Attenuation of adverse effects
- Improved patient compliance.

The extent of fluctuation in drug concentration at steady state is determined by the relative magnitude of the elimination half-life and the dosing interval. If a drug is

given at an interval equal to the elimination half-life, there is a two-fold difference between the maximum and minimum concentrations at steady state.

For drugs with short half-lives and with a clear relationship between concentration and response, it will be necessary to dose at regular, frequent intervals in order to maintain the concentration within the therapeutic range. Higher doses at less frequent intervals will result in higher peak concentrations with the possibility of toxicity. For some drugs with wide margins of safety, this approach may be satisfactory, e.g. amoxycillin has a half-life of approximately one hour, but a dosage frequency of 8 hours. This means that very large fluctuations will occur within a dosing interval, but, in view of the low toxicity of this drug, no difficulty with this approach is encountered provided the concentrations are above the minimum effective concentration during the dosing interval. On the contrary, clinical efficacy may be enhanced by the transiently high bactericidal concentration of the antibiotic e.g. aminoglycosides.

Conversely, drugs with long half-lives can be given at less frequent intervals. There is generally no advantage in formulating these drugs as extended-release formulations unless a rapid rate of change of concentration during the absorptive phase is responsible for transient adverse effects. The pharmacological effect of some drugs with short half-lives is sustained by various mechanisms: [6]

- The drug binds to the tissues e.g. tissue-bound ACE inhibitors. For these drugs, less frequent dosing is needed even though the drug may have a short half-life
- the drugs have irreversible effects e.g. the inhibition of platelet cyclo-oxygenase by aspirin
- the relationship between response and plasma/blood concentrations is relatively flat or if the dose given results in concentrations which are in the plateau region of the dose-response relationship e.g. thiazides in hypertension
- The drug is metabolised to pharmacologically active metabolite(s) which are more slowly cleared than the parent drug e.g. quinapril, trandolapril, venlafaxine.

Types of Extended Release Products:

- Diffusion-controlled products
- Dissolution-controlled products

- Erosion products
- Osmotic pump systems
- Ion exchange resins

1.4 HYPERTENSION [7]

Hypertension (**HTN** or **HT**), also known as **high blood pressure** (**HBP**), is a long term medical condition in which the blood pressure in the articles is persistently elevated. High blood pressure usually does not cause symptoms. Long term high blood pressure, however, is a major risk factor for coronary artery disease, stroke, heart failure, peripheral vascular disease, vision loss, and chronic kidney disease.

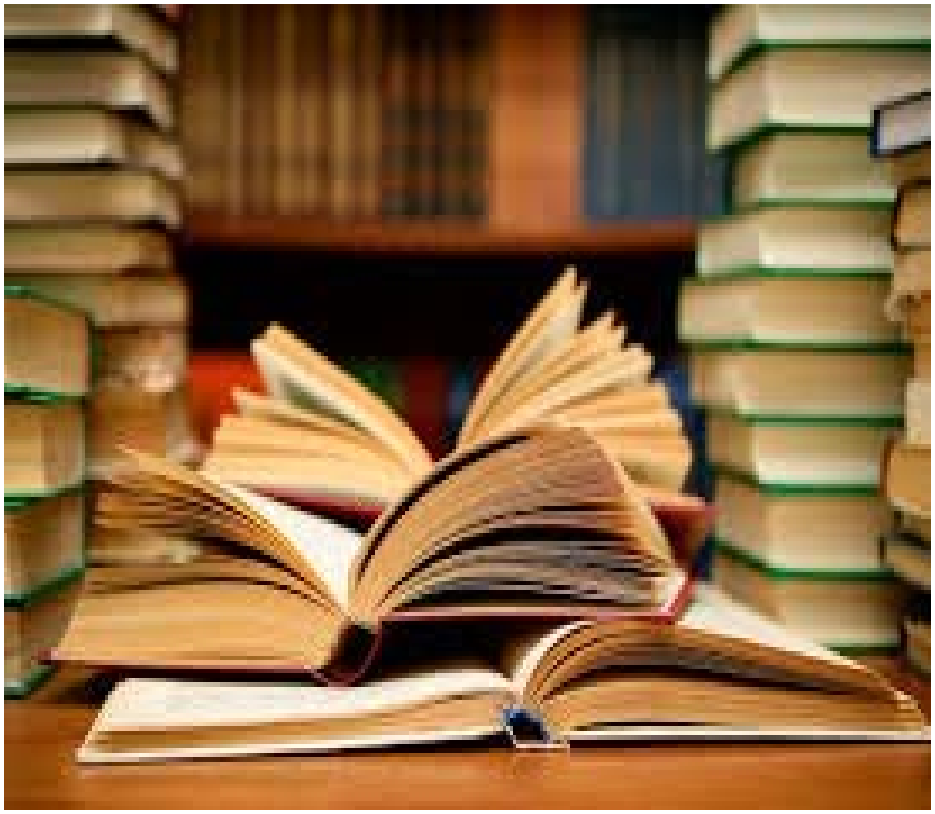
High blood pressure is classified as either Primary (essential) high blood pressure or secondary high blood pressure. About 90–95% of cases are primary, defined as high blood pressure due to nonspecific lifestyle and genetic factors. Lifestyle factors that increase the risk include excess salt, excess body weight, smoking and alcohol. The remaining 5–10% of cases are categorized as secondary high blood pressure, defined as high blood pressure due to an identifiable cause, such as chronic kidney disease, narrowing of the kidney arteries, an endocrine disorder, or the use of birth control pills.

Blood pressure is expressed by two measurements, the systolic and diastolic pressures, which are the maximum and minimum pressures, respectively. Normal blood pressure at rest is within the range of 100–140 millimeters mercury (mmHg) systolic and 60–90 mmHg diastolic. High blood pressure is present if the resting blood pressure is persistently at or above 140/90 mmHg for most adults. Different numbers apply to children. Ambulatory blood pressure monitoring over a 24-hour period appears more accurate than office best blood pressure measurement.

Lifestyle changes and medications can lower blood pressure and decrease the risk of health complications. Lifestyle changes include weight loss, decreased salt intake, physical exercise, and a healthy diet. If lifestyle changes are not sufficient then blood pressure medications are used. Up to three medications can control blood pressure in 90% of people. The treatment of moderately high arterial blood pressure (defined as >160/100 mmHg) with medications is associated with an improved life expectancy. The effect of treatment of blood pressure between 140/90 mmHg and

160/100 mmHg is less clear, with some reviews finding benefit and others finding a lack of evidence for benefit. High blood pressure affects between 16 and 37% of the population globally. In 2010 hypertension was believed to have been a factor in 18% of all deaths (9.4 million globally).

Hence, in the present study, I have taken the anti-hypertension drug metoprolol succinate equivalent to metoprolol tartrate and formulated as extended release tablets with swellable polymers such as HPMC K_{100M}, HPMC K_{4M} by wet granulation method.



LITERATURE REVIEW

2. LITERATURE REVIEW

1. Ranjani V. Nellore, Gurvinder Singh Rekhi *et al.,* (2008) developed model extended release (ER) matrix tablet formulations for metoprolol tartrate (100 mg) sufficiently sensitive to manufacturing variables and to serve as the scientific basis for regulatory policy development on scale-up and post approval changes for modified-release dosage forms (SUPAC-MR). Several grades and levels of hydroxypropyl methylcellulose (Methocel K4M, K15M, K100M and K100LV), fillers and binders were studied. Three granulation processes were evaluated; direct compression, fluid-bed or high-shear granulation.

2. Jaleh Varshosaz, N. Tavakoli *et al.,* (2007) prepared metoprolol tartrate sustained release tablets (100 mg) using xanthan/guar gums, HPMC and CMC polymers by direct compression method. Results showed that natural gums were suitable for production of sustained release tablets of metoprolol.

3. H. Ravishankar, P. Patil *et al.,* (2008) described a modulated release, multiunit oral drug delivery technology using a system based on ionic interactions of anions of salts with quaternary ammonium ions of the ammoniomethacrylate polymer. The system consisted of a drug layered, EUDRAGIT® NE-coated salt core which was further coated with EUDRAGIT® RS. The relative effects of different anions on the polymer permeability have been investigated by studying their influence on the in vitro drug release.

4. Goyal, P. Shukla, A. K. Shrivastav investigated the factors influencing the release characteristics of drug substances from hydrophilic polymer matrix tablet using various hydrophilic polymers as polyethylene oxide (PEO), hydroxyethyl cellulose (HEC) and xanthan gum. Results concluded that best sustained release tablet could be produced using PEO along with HEC as hydrophilic controlling polymer.

5. Gothi G.D., Parikh B.N., *et al.*, (2010) made an attempt to reduce the frequency of dose administration, to prevent nocturnal heart attack and to improve the patient

Compliance by developing extended release (ER) matrix tablet of Metoprolol Succinate. They studied effect of concentration of hydrophilic (Eudragit) on the release rate of Metoprolol succinate.

6. Y.S.R. Krishnaiah, R.S. Karthikeyan, *et al.,* (2009) designed oral controlled drug delivery systems for highly water-soluble drug, metoprolol tartrate using guar gum as a carrier in the form of a three-layer matrix tablet. Matrix tablets containing either 30 (M1), 40 (M2) or 50% (M3) of guar gum were prepared by wet granulation technique using starch paste as a binder. Three-layer matrix tablets of metoprolol tartrate were prepared by compressing on both sides of guar gum matrix tablet granules of metoprolol tartrate M1, M2 or M3 with either 50 (TL1M1, TL1M2 or TL1M3) or 75 mg (TL2M1, TL2M2 or TL2M3) of guar gum granules as release retardant layers.

7. Y.S.R. Krishnaiah, R.S. Karthikeyan, *et al.,* (2008) designed oral controlled drug delivery systems for highly water-soluble drugs using guar gum as a carrier in the form of three-layer matrix tablets. Trimetazidine dihydrochloride was chosen as a model drug because of its high water solubility. The results indicated that guar gum, in the form of three-layer matrix tablets, is a potential carrier in the design of oral controlled drug delivery systems for highly water-soluble drugs such as trimetazidine dihydrochloride.

8. S.M. Al-Saidan, Y.S.R. Krishnaiah, *et al.,* (2009) carried out pharmacokinetic evaluation of oral controlled release formulation (guar gum-based three layer matrix tablets) containing highly soluble metoprolol tartrate as a model drug. The results of the study indicated that guar gum three-layer matrix tablets were able to provide oral controlled delivery of highly water-soluble drug such as metoprolol tartrate in humans.

9. M. R. Siahi, M. B. Jalali *et al.,* (2010) designed oral controlled drug delivery systems for the water soluble drug, verapamil hydrochloride, using natural and semisynthetic polymers as carriers in the forms of 1- and 3-layer matrix tablets. 3-layer matrix tablets

were prepared by compressing the polymers as release retardant layers on both sides of the core containing the drug.

10. Cherng-ju Kim evaluated triple layer, donut-shaped tablets (TLDSTs) for extended release dosage forms. TLDSTs were prepared by layering 3 powders sequentially after pressing them with a punch. The core tablet consisted of enteric polymers, mainly hydroxyl propyl methyl cellulose acetate succinate, and the bottom and top layers were made of a water-insoluble polymer, ethyl cellulose. He summarized, a TLDST was a good design to obtain zero-order or nearly zeroorder release kinetics for a wide range of drug solubilities.

11. M. C. Gohel, S. H. Bariya developed venlafaxine hydrochloride layered tablets using xanthan gum in the middle and barrier layers by wet granulation technique. Substantial water uptake and gelling of xanthan gum appears to be responsible for sustaining drug release.

12. Gohel M.C *et al.,* **(2009)** fabricated modified release tablet of metoprolol succinate using hydroxypropyl methylcellulose (HPMC) and xanthan gum as a matrixing agent. A 3^2 full factorial design was employed for the optimization of formulation. The percentage drug released at a given time (Y_{60}, Y_{240} and Y_{720}) and the time required for a given percentage of drugs to be released ($t_{50\%}$) were selected as dependent variables. The *in vitro* drug dissolution study was carried out in pH 6.8 phosphate buffer employing paddle rotated at 50 rpm. The similarity factor (f_2) was calculated for selection of best batch considering mean *in vitro* dissolution data of Seloken® XL as a reference profile. It is concluded that the desired drug release pattern can be obtained by using a proper combination of HPMC (high gelling ability) and xanthan gum (quick gelling tendency). The economy of xanthan gum and faster hydration rate favours its use in modified release tablets. The matrix integrity during dissolution testing was maintained by using hydroxypropyl methylcellulose.

13. Shishoo C.J *et al.,* **(2002)** evaluated In vitro - in vivo correlation of modified release formulations of theophylline. As part of our ongoing study an experimental modified

release capsule formulation, containing theophylline (200 mg) loaded microspheres (Formulation F4), was developed, characterised and its in vitro and in vivo performance was then compared with that of the three market modified release formulations of theophylline (200 mg)- two tablets (Formulations F2 and F3) and one capsule (Formulation F1). Formulation F1, F2 and F3 were analysed to find out the best market sample with acceptable bioavailability. All the four formulations were evaluated for in vitro theophylline release using different dissolution test conditions. In vitro studies indicated that only formulation F1 showed pH-dependent drug release while the other three formulations, including experimental formulation F4, showed almost condition-independent dissolution behaviour. The bioavailability studies indicated that amongst the market formulations (F1, F2, and F3), formulation F1 and F2 were bioequivalent but F3 failed to demonstrate acceptable dissolution and bioavailability.

14. Panchagnula R *et al.,* **(2007)** studied an in vitro evaluation of modified release formulations, marketed in India was conducted and compare their performance with a novel matrix- based multi particulate system. The results indicate that even though the marketed formulations are found to comply to the definition of modified release formulations and predicted to produce therapeutic blood level for a prolonged period of time, the fluctuations were expected to be found uncontrolled expect in the osmotic systems and matrix based multi particulate system. Thus it was concluded that novel matrix- based multi particulate systems were found to be superior to any other marketed formulations with respect to the therapeutic advantage as well as manufacturing feasibility.

15. Farrukh Z *et al.,* **(2010)** evaluated modified-release multiple-unit tablets of loratadine and pseudoephedrine hydrochloride. The immediate-release pellets containing pseudoephedrine hydrochloride alone or in combination with loratadine were prepared using extrusion– spheronization method. The pellets of pseudoephedrine hydrochloride were coated to prolong the drug release up to 12 h. Both immediate- and prolonged-release pellets were filled into hard gelatin capsule and also compressed into tablets using inert tabletting granules of microcrystalline

cellulose Ceolus KG-801. The *in vitro* drug dissolution study conducted using high-performance liquid chromatography method showed that both multiple-unit capsules and multiple-unit tablets released loratadine completely within a time period of 2 h, whereas the immediate-release portion of pseudoephedrine hydrochloride was liberated completely within the first 10 min of dissolution study. On the other hand, the release of pseudoephedrine hydrochloride from the prolonged release coated pellets was prolonged up to 12 hr and followed zero-order release kinetic. The drug dissolution profiles of multiple-unit tablets and multiple-unit capsules were found to be closely similar, indicating that the integrity of pellets remained unaffected during the compression process. Moreover, the friability, hardness, and disintegration time of multiple-unit tablets were found to be within BP specifications. In conclusion, modified release pellet-based tablet system for the delivery of loratadine and pseudoephedrine hydrochloride was successfully developed and evaluated.

16. Gohel M. C *et al.,* **(2008)** evaluated to prepare novel modified release press coated tablets of venlafaxine hydrochloride. Hydroxy propyl methylcellulose K4M and hydroxy propyl methylcellulose K100M were used as release modifier in core and coat, respectively. A 3^2 full factorial design was adopted in the optimization study. The drug to polymer ratio in core and coat were chosen as independent variables. The drug release in the first hour and drug release rate between 1 and 12 h were chosen as dependent variables. The tablets were characterized for dimension analysis, crushing strength, friability and *in vitro* drug release. The tablets of check point batch were subjected to *in vitro* drug release in dissolution media with pH 5, 7.2 and distilled water. The kinetics of drug release was best explained by Korsmeyer and Peppas model (anomalous non-Fickian diffusion). The systematic formulation approach enabled us to develop modified release venlafaxine hydrochloride tablets.

17. Gohel M. C *et al.,* **(1999)** studied the preparation of microspheres of diclofenac sodium using cross-linked poly (vinyl alcohol) (PVA). A central composite design consisting of a two-level full factorial design superimposed on a star design was employed for developing the microspheres. The PVA to the drug ratio X_1 and amount of glutaraldehyde cross-linking agent X_2 were chosen as the independent variables.

The time required for 50% drug dissolution t_{50} in phosphate buffer (pH 7.2) was selected as the dependent variable. An optimum polynomial equation was generated for the prediction of the response variable t_{50}. Based on the results of multiple linear regression analysis and *F* statistics, it may be concluded that sustained action can be obtained when X_1 and X_2 are kept at high levels. The X_1X_2 interaction was found to be statistically significant. A response surface plot is presented to show the effects of X_1 and X_2on t_{50}. The drug release pattern fit the Higuchi model well. A model was validated for accurate prediction of the drug dissolution profile with constraints on the percentage drug release in the first, fifth, and seventh hours. The data of a selected batch were subjected to an optimization study, and an optimal formulation was fabricated. Good agreement was observed between the predicted and the observed dissolution profiles of the optimal formulation.

18. Gohel M. C *et al.,* **(2007)** developed modified release tablets of isoniazid using hydroxylpropylmethycellulose as a release-controlling agent. The low-viscosity grade hydroxylpropylmethycellulose, medium-viscosity grade hydroxylpropylmethy cellulose, and high-viscosity grade hydroxylpropylmethycellulose were used to prepare the matrix tablets**.** The tablets are prepared by direct compression, were subjected to physical characterization and in vitro drug release studies. The in vitro drug release was carried using USP 1 at 50 rpm in 900 ml of acidic dissolution medium (pH 1.2) for 2 h, followed by 900 ml of alkaline dissolution medium (pH 6.8). The polymer type did not affect the flow of powder blend and crushing strength of isoniazid tablets. The drug release rate was strongly influenced by the type of polymer and concentration of polymer. The viscosity grade of hydroxylpropylmethycellulose and the drug release was inversely correlated.

19. Sahib M.N *et al.,* **(2009)** fabricated prednisolone as an oral modified release tablet for colonic targeting. Many trials were performed to prepare a satisfactory formula using wet granulation method with various additives and coatings. We found that lactose as diluents provided the most reasonable relsease for prednisolone among other diluents. In addition the formula containing 1 % Eudragit RS PM was the best with regard to 100% release of drug in comparison to other concentrations and other

retardant types. Avicel was used as a canalising agent and, the result show that the formula containing 30%Avicel PH 302 demonstrated faster release. Eudragit S 100 provided the best release in phosphate buffer, pH 7.4. The effect of present of binding agent polyvinylpyrrolidone (PVP) (5%, 10% and 15%) was studied, and the best results were obtained with the concentration of 10%. The trials in this study successfully formulated prednisolone-modified release tablets (coated matrix) using a wet granulation method as a potential colon delivery system.

20. Avramoff A *et al.,* **(2010)** evaluated the in-vitro dissolution and in-vivo pharmacokinetic profile of a novel two-phase modified-release formulation for diltiazem hydrochloride, as a water-soluble drug. The delivery system consisted of two tablets inserted into a capsule. Both tablets comprised a coated drug core-matrix. Three different formulations were tested for their dissolution profiles both in water media and in buffer with a pH of 6.8. These formulations were also evaluated for their pharmacokinetic profile in healthy volunteers after single administration of a 240 mg dosing addition the in-vivo /in-vitro correlation (IVIVC) was calculated for these formulations. The in-vitro characteristics of these formulations demonstrated a controlled release profile in both media but with different characteristics, as in Formulation 3 where faster dissolution profile obtained in water but slower one in pH 6.8 buffer. In-vivo the pharmacokinetic profile of these formulations showed that arabinogalactan containing formulations achieved plasma levels which allow a once daily administration. IVIVC calculation demonstrated that dissolution tested in buffer 6.8 media better correlates with the percent absorbed in-vivo and the best results were achieved with the formulation containing the highest amount of polysaccharide in the coating. It is concluded that the developed formulations achieved a controlled release profile both in-vitro and in-vivo which are suitable for once-daily administration.

21. Gohel M. C *et al.,* **(2003)** showed the preparation of tartaric acid treated ispaghula husk powder for the development of modified release tablets of diltiazem HCl by adopting direct compression technique and a 3^2 full factorial design. The modified ispaghula husk powder showed superior swelling and gelling as compared to

untreated powder. Addition of compaction augmenting agent such as dicalcium phosphate was found to be essential for obtaining tablets with adequate crushing strength. In order to improve the crushing strength of diltiazem HCl tablets, to modulate drug release pattern, and to obtain similarity of dissolution profiles in distilled water and simulated gastric fluid (pH 1.2), modified guar gum was used along with modified ispaghula husk powder and tartaric acid. A novel composite index, which considers a positive or a negative deviation from an ideal value, was calculated considering percentage drug release in 60, 300, and 540 min as dependent variables for the selection of a most appropriate batch. Polynomial equation and contour plots are presented. The concept of similarity factor (f2) was used to prove similarity of dissolution in water and simulated gastric fluid (pH 1.2).

22. Abdelbary G *et al.,* **(2008)** developed an extended release matrix tablet of nicorandil; a freely water soluble drug used in cardiovascular diseases. Chitosan (CH)/hyaluronate sodium (HA), pectin (PE) or alginate sodium (AL) interpolymer complexes (IPCs) were prepared. The optimum IPCs (CH: HA, 40:60), (CH: PE, 30:70) and (CH: AL, 20:80) were characterized by Fourier transform infrared spectroscopy. The IPCs were based on electrostatic interactions between protonated amine groups of CH and carboxylate groups of HA, PE or AL. Nicorandil matrix tablets were prepared using the optimum IPCs, alone or in combination with Imwitor_ 900 K. Evaluations such as weight variation, thickness, content uniformity, friability, disintegration and in vitro release studies were performed. The tablets showed acceptable pharmacotechnical properties and complied with compendial requirements. Results of the dissolution studies revealed that formula F11 (CH: AL, 20:80) IPC: Imwitor_ 900 K, 3:1) could extend drug release >8 h. Most formulae exhibited non-Fickian diffusion drug release profiles. When compared to the immediate release Ikorel_ tablet, the duration of effective nicorandil therapeutic concentration from formula F11, in healthy human volunteers, was significantly ($P < 0.05$) extended from 4 to 8 h with expected lowering in side effects potential.

23. Limmatvapirat S *et al.,* **(2008)** designed a new oral controlled release matrix tablet based on shellac polymer using metronidazole (MZ) as a model drug. The shellac-

based matrix tablets were prepared by wet granulation using different amounts of shellac and lactose. The effect of annealing temperature and pH of medium on drug release from matrix tablets was investigated. The increased amount of shellac and increased annealing temperature significantly affected the physical properties (i.e., tablet hardness and tablet disintegration) and MZ release from the matrix tablets. The in-situ polymerization played a major role on the changes in shellac properties during annealing process. Though the shellac did not dissolve in acid medium, the MZ release in 0.1 N HCl was faster than in pH 7.3 buffer, resulting from a higher solubility of MZ in acid medium. The modulation of MZ release kinetics from shellac-based matrix tablets could be accomplished by varying the amount of shellac or annealing temperature. The release kinetics was shifted from relaxation-controlled release to diffusion-controlled release when the amount of shellac or the annealing temperature was increased.

24. Corti G *et al.,* **(2008)** developed a MH sustained-release formulation in compliance with these requirements. The strategy proposed is based on direct-compressed matrix tablets consisting of a combination of MH with the hydrophobic triacetyl-b-cyclodextrin (TAbCD), dispersed in a polymeric material. Different polymers were tested as excipients, i.e. hydroxylpropylmethycellulose, xanthan gum, chitosan, ethyl cellulose, Eudragit_L100-55, and Precirol_. Release studies demonstrated that blends of a hydrophobic swelling polymer (hydroxylpropylmethycellulose or chitosan) with a pH-dependent one (Eudragit_L100-55) were more useful than single polymers in controlling drug release. Moreover, the main role played by the MH–TAbCD system preparation method (i.e. grinding or spray drying) in determining the behaviour of the final formulation was evidenced. In particular, the 1:1 (w/w) blend of such systems, dispersed in a Eudragit–chitosan polymeric matrix, fully achieved the prefixed goal, giving about 30% released drug after 2 h at gastric pH, and overcoming 90% released drug within the subsequent 3 h in jejunal fluid.

25. Tanaka N *et al.,* **(2005)** developed a novel sustained-release (SR) system for poorly water soluble drugs by applying solid dispersion (SD) technique for improving the solubility. The developed SR system, disintegration-controlled matrix tablet (DCMT),

consists of hydrogenated soybean oil (HSO) as wax and SD granules containing low-substituted hydroxypropylcellulose (L-HPC) as a disintegrant. In this study, nilvadipine (NiD) was chosen as a model compound.

Sustained-release profiles of NiD from DCMT were identically controlled in several dissolution mediums in spite of varying pH and agitation speed. The release of NiD from DCMT was sustained more effectively by increasing the amount of wax or by decreasing the amount of disintegrant, and supersaturation of NiD was achieved without any re-crystallization in dissolution medium. The release rate of NiD from DCMT was controlled by the disintegration rate of tablet. The release profile of NiD was described by the Hixson– Crowell's model better than zero-order kinetics, first-order kinetics and Higuchi's model, which supports that the release of NiD from DCMT is regulated by the disintegration of the tablet. From this study, it was clarified that DCMT was one of the promising SR systems applying SD for the poorly water soluble drugs.

26. Jain A *et al.,* **(2011)** Studied the review on floating drug delivery systems (FDDS) was to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery systems (FDDS), also known as hydro dynamically balanced systems (HBS), swelling and expanding systems, polymeric bio adhesive systems, modified-shape systems, high-density systems, and other delayed gastric emptying devices. From the formulation and technological point of view, the floating drug delivery system is considerably easy and logical approach. An attempt has been made in this review article to introduce the readers to the current technological developments in floating drug delivery System.

27. Thanoo B. C. *et al.,* **(2011)** Developed Polycarbonate microspheres loaded with aspirin, griseofulvin and *p*-nitroaniline were prepared by a solvent evaporation technique. High drug loading (> 50%) was achieved by this process. Drug-loaded microspheres were found to float on simulated gastric fluid and intestinal fluid. Drug-release studies were carried out in these fluids at 37°C. Increasing the drug to polymer

ratio in the microspheres increased both their mean particle size and the release rate of the drugs. It was concluded that sustained delivery of drugs could be effected using this matrix.

28. Patil P. N *et al.,* **(2011)** developed as floating drug delivery system (FDDS) for sustained release of cisapride using direct compression technology. Core contained low density, porous ethyl cellulose, which was coated with an impermeable, insoluble hydrophobic coating polymer such as rosin. It was further seal coated with low viscosity hydroxypropyl methyl cellulose (HPMC E15) to minimize moisture permeation and better adhesion with an outer drug layer. It was found that stable buoyant core was sufficient to float the tablet more than 8 h without the aid of sodium bicarbonate and citric acid. Sustained release of cisapride was achieved with HPMC K4M in the outer drug layer. The floating lag time required for these novel FDDS was found to be zero, however it is likely that the porosity or density of the core is critical for floatability of these tablets. The in vitro release pattern of these tablets in simulated gastric fluid showed the constant and controlled release for prolonged time. It can be concluded that the hydrophobic coated buoyant core could be used as FDDS for gastro retentive delivery system of cisapride or other suitable drugs.

29. Raja R *et al.,* **(2011)** developing a modified release hydrogel formulation of poorly soluble drug, Gliclazide using a retardant hydrophilic polymer HPMC in two grades i.e., HPMC 15 cps and Methocel K4M. All six formulations were developed and evaluated for the in-vitro drug release up to 16hrs and compared with that of the marketed formulation. GMF VI was found to have similar release pattern proving to show controlled release following zero order release by anomalous diffusion. The similarity and Dissimilarity factors were found to be 1.12 and 93.99 respectively. Thus the formulation was found to be advantageous in reducing the dosing intervals and enhancing the patient compliance.

30. **Lassalle V** *et al.,* **(2010)** developed Drug delivery systems (DDS) using insulin as model drug and poly (lactic–co-glycolic) copolymers (PLGA) as polymeric matrix. The carriers were synthesized by direct self-assembly of the insulin and the polyester

under mild conditions. In vitro release studies demonstrated that copolyesters of about 8600 and 1500 Da were suitable for the gradual release of insulin while PLGA oligomers of average molecular weight between 700 and 800 Da were unsuitable as DDS. The insulin release kinetics fits well with the Korsmeyer model, following the anomalous transport mechanism.

31. Gupta B. P., (2010) studied conventional drug delivery systems have slight control over their drug release and almost no control over the effective concentration at the target site. This kind of dosing pattern may result in constantly changing, unpredictable plasma concentrations. Drugs can be delivered in a controlled pattern over a long period of time by the controlled or modified release drug delivery systems. They include dosage forms for oral and transdermal administration as well as injectable and implantable systems. For most of drugs, oral route remains as the most acceptable route of administration. Certain molecules may have low oral bioavailability because of solubility or permeability limitations. Development of an extended release dosage form also requires reasonable absorption throughout the gastro-intestinal tract (GIT). Among the available techniques to improve the bioavailability of these drugs fabrication of osmotic drug delivery system is the most appropriate one. Osmotic drug delivery systems release the drug with the zero order kinetics which does not depend on the initial concentration and the physiological factors of GIT. This review brings out new technologies, fabrication and recent clinical research in osmotic drug delivery.

AIM AND OBJECTIVE

3. AIM AND OBJECTIVE

AIM:

The aim of the work is to design and develop extended release tablets comprising of Metoprolol succinate equivalent to Metoprolol tartrate by wet granulation method using swellable polymers such as HPMC K_{100M}, HPMC K_{4M} and to carry out the *In vitro* release study of the drug.

OBJECTIVES:

The **Pharmaceutical Formulation** objectives which were destined to achieve during the work are:

- Extended release tablets with good physical strength.
- Tablets with optimum content of active pharmaceutical ingredients without variation in the content unit/tablet.

The **Pharmacological** objectives which were destined to achieve during the work are:

- To maintain the drug concentration within the therapeutic range, there would be a need of administration of drug for more than once a day.
- To improve the patient compliance and avoid frequency of dosing intervals.
- To provide effective, Safe and stable pharmaceutical oral formulation containing Prolonged release of Antihypertension drugs with mechanism of action to improve Blood Pressure control.

PLAN OF WORK

4. PLAN OF WORK

- Raw Material Analysis
- Preformulation studies
- Compatibility studies
- Formulation of ER Tablets.
- Evaluation of Extended Release Tablets.

5. DRUG PROFILE

Metoprolol Succinate

Metoprolol Succinate is a beta1-selective (cardioselective) adrenoceptor blocking agent, for oral administration, available as extended-release tablets. Metoprolol Succinate extended-release tablets has been formulated to provide a controlled and predictable release of metoprolol for once-daily administration. The tablets comprise a multiple unit system containing metoprolol succinate in a multitude of controlled release pellets. Each pellet acts as a separate drug delivery unit and is designed to deliver metoprolol continuously over the dosage interval. The tablets contain 23.75, 47.5, 95 & 190mg of metoprolol succinate equivalent to 25, 50, 100 & 200mg of metoprolol tartrate USP respectively. This preferential effect is not absolute, however and at higher plasma concentrations, metoprolol also inhibits beta2-adrenoreceptors, chiefly located in the bronchial & vascular musculature. Metoprolol has no intrinsic sympathomimetic activity & membrane-stabilizing activity is detectable only at plasma concentrations much greater than required for beta-blockade.

Metoprolol succinate extended-release tablets produced an improvement in left ventricular ejection fraction. It was also shown to delay the increase in left ventricular end-systolic & end-diastolic volumes after 6 months of treatment.

IUPAC Name	:	1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]- 2-Propanol succinate.
Molecular Weight	:	652.8 g/mol.
Molecular formula	:	$C_{15}H_{25}NO_3$
Therapeutic class	:	Hypotension, Angina pectoris, Myocardial Infraction.
Dose	:	100mg once daily.

PROPERTIES

Description	:	White coloured crystalline powder.
Solubility	:	Freely soluble in water, soluble in methanol, sparingly Soluble In ethanol, insoluble in ethyl acetate, acetone, Diethylether & Heptane.
Melting point	:	120^0C
Heavy metals	:	Not more than 20ppm
Sulphated ash	:	Not more than 0.1%
Loss on drying	:	Not more than 0.5%, determined on 1gm by drying in an Oven at 105^0C.
Storage	:	Store in well-closed container.
Shelf life	:	36 Months

CLINICAL PHARMACOLOGY

Clinical pharmacology studies have confirmed the beta-blocking activity of metoprolol in man, as shown by

1. Reduction in heart rate & cardiac output at rest upon exercise.
2. Reduction of systolic blood pressure upon exercise.
3. Inhibition of isoproterenol-induce tachycardia.
4. Reduction of reflex orthostatic tachycardia.

Pharmacokinetics

In man, absorption of metoprolol is rapid and complete. Plasma levels following oral administration of conventional metoprolol tablets, however, approximate 50% of levels following IV administration, indicating about 50% first-pass metabolism. Metoprolol crosses the BBB and has been reported in the CSF in a concentration 78% of the simultaneous plasma concentration. Plasma levels achieved are highly variable after oral administration. Only a small fraction of the drug (about 12%) is bound to human serum albumin. Its primarily metabolised by CYP2D6. Elimination is mainly by biotransformation in the liver and the plasma half-life ranges from approximately 3 to 7 hours.

MECHANISM OF ACTION

1. Competitive antagonism of catecholamine at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output.
2. A central effect leading to reduced sympathetic outflow to the periphery.
3. Suppression of renin activity.

Laboratory test findings

Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphate and lactate dehydrogenase.

Drug Interactions

Catecholamine depleting drugs (eg, Reserpine, Monoamine oxidase (MAO) inhibitors) may have an additive effect when given with beta blocking agents. Observe patients treated with Metoprolol succinate extended release tablets plus a catecholamine depletory for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope or postural hypotension.

Dosage information

Overdosage of Metoprolol succinate extended release tablets may lead to bradycardia, hypotension & cardiogenic shock. Clinical presentation can also include atrioventricular block, heart failure, bronchospasm, hypoxia, impairment of consciousness/coma, nausea and vomiting.

Treatment

Consider treating the patient with intensive care. Patients with myocardial infraction or heart failure may be prone to significant hemodynamic instability. Seek consultation with a regional poison control center & a medical toxicologist as needed. Beta-blocker overdose may result in significant resistance to resuscitation wit adrenergic agents, including beta-agonists. On the basis of the pharmacological actions of Metoprolol, employ the following measures. There is very limited experience with the use of haemodialysis to remove Metoprolol, however Metoprolol is not highly protein bound.

6. EXCIPIENT PROFILE

HYDROXY PROPYL METHYL CELLULOSE:

1. **Non-proprietary Names**

   BP: Hypromellose, JP: Hypromellose, PhEur: Hypromellose, USP: Hypromellose

2. **Synonyms**

   Hydroxy propyl methyl cellulose, HPMC, Hypromell sum, Methocel, Methyl cellulose propylene glycol ether, Methyl hydroxy propyl cellulose, Metolose.

3. **Chemical Name**

   Cellulose hydroxyl propyl methyl ether

4. **Functional Category**

   Bio adhesive material, coating agent, controlled-release agent, dispersing agent, dissolution enhancer, emulsifying agent, emulsion stabilizer, extended-release agent, film forming agent, foaming agent, granulation aid, modified-release agent, muco-adhesive, release modifying agent, solubilizing agent, stabilizing agent, suspending agent, sustained release agent, tablet binder, thickening agent, viscosity-increasing agent.

5. **Applications in Pharmaceutical Formulation or Technology:**

   In oral products, hypromellose is primarily used as a tablet binder, film-coating, and as a matrix for use in extended-release tablet formulations. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80%w/w in tablets and capsules.

6. **Description:**

   Hypromellose is an odourless and tasteless, white or creamy-white fibrous or granular powder.

7. **Typical Properties**.

   Acidity/alkalinity pH=5.0–8.0 for a 2%w/w aqueous solution.

   Ash ≤1.5%

   Density (bulk) 0.341g/ml

Density tapped) 0.557g/ml

Melting point: Browns at190–200ºC; chars at 225–230ºC.

Solubility: Soluble in cold water, forming a viscous colloidal solution.

POVIDONE K90:

1. **Non-proprietary Names**

BP	:	Povidone
JP	:	Povidone
PhEur	:	Povidone
USP	:	Povidone

2. **Synonyms**

Kollidon, Plasdone, poly [1-(2-oxo-1-pyrrolidinyl) ethylene], Polyvidone, Poly vinyl pyrrolidone, Povidonum, Povipharm, PVP; 1-vinyl-2-pyrrolidinone polymer.

3. **Chemical Name**

1-Ethenyl-2-pyrrolidinonehomopolymer

4. **Functional Category**

Disintegrant; dissolution enhancer; suspending agent; tablet binder.

5. **Applications in Pharmaceutical Formulation or Technology**

Povidone solutions are used as binders in wet-granulation processes. Povidone is also added to powder blends in the dry form and granulated in situ by the addition of water, alcohol, or hydro-alcoholic solutions.

6. **Description**

Povidone occurs as a fine, white to creamy white colored, odourless oral most odourless, hygroscopic powder.

7. **Typical Properties**

Acidity/alkalinity pH=3.0–7.0 (5%w/v aqueous solution);

Density (bulk):0.29–0.39g/ml

Density (tapped):0.39–0.54gml

Density (true):1.180g/ml

Melting point often at 150ºC

MICROCRYSTALLINE CELLULOSE:

1. **Non-proprietary**

   BP/ JP /USPNF : Microcrystalline cellulose

   PhEur : Cellulosum microcristallinum

2. **Synonyms**

   Avicel PH, Celexe, Cellulose gel, Celphere, Ceolus KG, Crystalline cellulose, Emcocel, Ethispheres, Fibrocel, Pharmacel, Tabulose, and Vivapur.

3. **Chemical Name** Cellulose.

4. **Description**

   Colour : White.

   Nature : Crystalline powder composed of porous particles.

5. **Typical Properties**

   Angle of repose : 49° for Ceolus KG.

   Density (bulk) : 0.337 g/cm3.

6. **Functional Category**

   Adsorbent, suspending agent, tablet and capsule diluent, tablet disintegrant.

Applications MCCPpH102 in Pharmaceutical Formulation

Use	Concentration (%)
Adsorbent	20–90
Antiadherent	5–20
Capsule binder/diluent	20–90
Tablet disintegrant	5–15
Tablet binder/diluent	20–90

COLLOIDAL SILICON DIOXIDE:

1. Non-proprietary Names

BP : Colloidal anhydrous silica

PhEur : Silica colloidalis anhydrica

USPNF : Colloidal silicon dioxide

2. Synonyms

Aerosil, Cab-O-Sil, Cab-O-Sil M-5P, colloidal silica, fumed silica, light anhydrous silicic acid, silicic anhydride, silicon dioxide fumed, Wacker HDK.

3. Chemical Name: Silica

4. Description

Colour: Bluish-White.

Nature : Nongritty amorphous, particle size: 15 nm.

5. Typical Properties

Acidity/alkalinity: pH = 3.5–4.4 (4% w/v aqueous dispersion)

Bulk Density : 0.029–0.042 g/cm3

Carr's index : 35.52%

Solubility: Practically insoluble in organic solvents, water, and acids, except hydrofluoric acid, soluble in hot solutions of alkali hydroxide. Forms a colloidal dispersion with water.

6. Functional Category

Adsorbent, Anticaking agent, Emulsion stabilizer, Glidant, Suspending agent, Tablet disintegrant, Thermal stabilizer, Viscosity-increasing agent.

7. Applications in Pharmaceutical Formulation or Technology

Aerosols 0.5–2.0%, Emulsion stabilizer 1.0–5.0%, Glidant 0.1–0.5%, Suspending and thickening agent 2.0–10.0%.

MATERIALS & METHODS

7. MATERIALS AND METHODS

Table No.1 List of Materials and their applications in Formulation

S. No	Name of the materials	Manufacturer / Supplier	Use in Formulation
1.	Metoprolol Succinate	Maan Medex Private, Nagpur.	Active ingredient
2.	HPMC K 100 M	Colourcon Asia Ltd, Mumbai.	Hydrophilic Polymer
3.	HPMC K 4 M	Colourcon Asia Ltd, Mumbai.	Hydrophilic Polymer
4.	Lactose Monohydrate	Triveni Chemicals, Gujarat.	Hydrophilic Polymer
5.	Microcrystalline Cellulose PH 102	Ashutosh Chemicals, Delhi.	Hydrophilic polymer
6.	Povidone K – 90	Triveni Chemicals, Gujarat.	Binder
7.	Isopropyl Alcohol	Arrow Fine Chemical, Rajkot.	Binder
8.	Colloidal Silicon Dioxide	K.P Manish Global, Chennai.	Lubrication
9.	Sodium Stearyl Fumarate	Triveni Chemicals, Gujarat.	Lubrication
10.	Hypromellose (HPMC E-05)	Colourcon Asia Ltd, Mumbai.	Coating Material
11.	Titanium Dioxide	Shri Krishna Enterprises, Chennai.	Coating Material
12.	Purified Talc	Manidharma Biotech Pvt Ltd, Chennai.	Glidant
13.	Tween 80	Triveni Chemicals, Gujarat.	Coating Material
14.	Polyethylene glycol – 1500	A.B Enterprises, Mumbai.	Coating Material

Table No.2 Equipment used for formulation

S. No	Equipment	Manufacturer / Supplier
1.	Weighing balance-1	Mettler Toledo, Japan
2.	Dial caliper	Mitutoyo, Japan
3.	Pfizer Hardness tester	Cadmach, India
4.	Friability tester	Electro lab, Bombay
5.	pH meter	Symchrony, India
6.	Melting point apparatus	Inlab Equipment pvt.Ltd, Madras
7.	Hot air oven	Industrial heaters, chennai
8.	Disintegration apparatus	Electro lab, Mumbai.
9	Dissolution apparatus	Electro lab, Mumbai.
10.	Ultra-sonic cleaner	Sidilu, Ultro Sonics, India
11.	UV spectrophotometer – 1700	Shimadzu, Japan
12.	HPLC	Algient Technologies, Switzerland
15.	16 Station Compression machine	Cadmach, India
16.	Stability chamber	Inlay Scientific Instruments, India
17.	Tray Drier	Rays Scientifics instruments, India
18.	Moisture balance	Mettler Toledo, Japan
19.	Weighing Balance-2	Shimadzu, Japan
20.	Tab density tester	Electro lab, Mumbai.

7.1 Raw Material Analysis:

Description

Appearance of the material was noted compared with specified monograph or with standard materials.

Identification

Identification is the important parameter for Qualitative Analysis of materials. Material was identified by chemical and FT-IR method.

Solubility Analysis

Solubility is an important parameter for preformulation studies because:

1. It affects the dissolution of drug.
2. Bioavailability of drug is directly affected by dissolution and absorption of drug by oral administration.
3. Particle size, shape, surface area may affects the dissolution characteristics of drug hence it should be determined during Preformulation.

Table No.3 Solubility description

Descriptive Term	Approximate volume of solute in millilitres per gram of solute
Very Soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10000
Practically insoluble	More than 10000

Method: Appropriate quantity of drug was weighed and added to the suitable volume of solvent.

Loss on drying (%)

1g of drug was accurately weighed and dried in an oven at 105°C for 3 hours. By gentle sidewise shaking, the sample was distributed at the specified temperature for constant weight.

The drug sample was allowed to come to room temperature in a desiccator before weighing.[69] The difference between successive weights should not be more than 0.5mg The loss on drying is calculated by the formula:

$$\% \text{ LOD} = \frac{W3 - W2}{W2 - W1} \times 100$$

Where, W_1 – Weight of empty weighing bottle

W_2 – Weight of weighing bottle + sample

W_3 – Weight of weighing bottle + dried sample

Melting point determination

The melting point of Active ingredients were determined by capillary method, using definite quantity of Active ingredients were taken and placed in apparatus and melting point was determined and matched with standards.

Bulk density

The powder sample (blend) under test was screened through sieve #18 and the sample equivalent to 20gm was accurately weighed and filled in a 100ml graduated cylinder and the powder was leveled and the unsettled volume (V_0) was noted. The bulk density was calculated in g/cm^3 by the formula,

Bulk Density = Mass of the Powder / Volume

Purity

Purity of the sample was analyzed by using suitable method.

7.2 Preformulation Studies

Preformulation studies are the first step in the rational development of dosage form. It is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. Preformulation investigations are designed to identify those physicochemical properties and Excipients that may influence the formulation design, method of manufacture, and pharmacokinetic-biopharmaceutical properties of the resulting product. Following are the test performed for the preformulation study.

Drug and Drug – Excipient Physical Compatibility Studies:

The Active ingredients and excipients were mixed and taken in 2 ml glass vials and sealed. These glass vials are kept at Room Temperature and 40°C / 75 % RH for about 1 month. At the interval of 10 days, the samples were withdrawn and analyzed for colour change.

Drug and Drug – Excipient Chemical Compatibility Studies:

The successful formulation of a stable and effective dosage form depends on the careful selection of the excipients that are added to facilitate administration, promote the consistent release and Bioavailability of the drug and protect it from degradation. The excipients are selected by conducting compatibility studies with the APIs.

Procedure:

The APIs were mixed with some of the excipients that can be used for the formulation in the ratio of Drug: Excipient (1:1, 1:0.5). These are placed in stability chambers at conditions 25°C / 60 % RH and 40°C / 75 % RH for 30 days. The samples that were placed in 40°C / 75 % RH chambers were analysed with IR spectroscopy after 30 days. For IR studies Shimadzu FTIR (IR Prestige 21) was used. The IR spectroscopy graphs obtained were compared with standard graphs. Any possible interactions can be detected from changes in graphs of IR studies. The excipient that is causing a change will not be used in the formulation.

Containers:

- Containers and closures for the compatibility study are 10 ml flint glass vials (USP type I), Bromo butyl rubber stoppers and tears off clear lacquer aluminium seals.
- Remove vials from packaging and sort out the vials with defects like cracks, broken edges, air bubbles and reject them form using.
- Clean the vials by rising initially with potable water followed by rinsing with purified water.
- Dry the washed vials in hot air oven (70°C for 1 hour). Physically sort the washed and dried vials for any kind of defects like broken edges, cracks or air bubbles, white or black fibres/particles, foreign matter, etc and reject those vials.

Sample Preparation:

- Drug and excipients as per the ratio (1:1, 1:0.5) were prepared and placed with accurate amount of drug and excipients in a polybag and mixed.
- Then these samples were placed in separate flint glass vials. Then these samples were charged in stability chamber of conditions 40°C / 75 % RH and 25°C / 60 % RH.
- After 15 days and 30 days, samples were also seen for changes in the colour and odour (samples placed in both the conditions).

7.3 Formulation Development

Different batches of Metoprolol succinate Extended release layer ($F_1$to F_7) were prepared with varying concentrations of different formulation ingredients according to Table. Pass the all material in 80 mesh except MCCP pH102 and it was in 60 mesh. Mix well Metoprolol succinate, polymer, MCCP PH102, CSD then add binder solution Isopropyl alcohol to the mixer, Blend well to form a coherent mass and dried in oven. And pass the granules in 18 mesh. The granules were lubricated with Sodium Stearyl fumarate, Talc and CSD. The amount required for formulation is given for following Table.

Table No.4 Formula for ER Tablet formulation

Ingredients for 1 tablet	F1 mg	F2 mg	F3 mg	F4 mg	F5 mg	F6 mg	F7 mg
Metoprolol succinate	95	95	95	95	95	95	95
HPMC K100M	260	250	240	230	220	210	200
HPMC K4M	-	10	10	20	20	20	20
Lactose Monohydrate (200M)	80	80	80	80	80	80	80
Monocrystalline Cellulose PH 102	-	-	10	10	20	30	40
Povidone K-90	15	15	15	15	15	15	15
Isopropyl Alcohol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Colloidal Silicon Dioxide	6	6	6	6	6	6	6
Sodium Stearyl Fumarate	4	4	4	4	4	4	4
Total Weight	**460**	**460**	**460**	**460**	**460**	**460**	**460**

Table No.5 Coating Materials ER Tablet Formulation

Ingredients for 1 tablet	F1 mg	F2 mg	F3 mg	F4 mg	F5 mg	F6 mg	F7 mg
Hypromellose	9.5	9.5	9.5	9.5	9.5	9.5	9.5
Titanium Dioxide	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Purified Talc	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Tween 80	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Polyethylene glycol-1500	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Brilliant blue lake	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Isopropyl Alcohol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Methylene chloride	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

MANUFACTURING PROCESS:

1. Shifting:

Pass the ingredients through the below mentioned mesh size and collect separately.

Table No.6 Sieving process

S.NO	Ingredients	Mesh size	Microns
1.	Metoprolol succinate	30#	600
2.	HPMC K100M	20#	840
3.	HPMC K4M	20#	840
4.	Lactose Monohydrate	60#	250
5.	MCC PH 102	40#	420
6.	CSD	30#	600
7.	Sodium Stearyl fumarate	40#	420

2. Dry Mixing:

Load the sifted batch quantity materials in to the RMG by following sequence Metoprolol succinate, HPMC K100M, HPMC K4M, Lactose monohydrate and Microcrystalline Cellulose PH 102. Mix the materials by running impeller at slow speed for 10 minutes and chopper off.

3. Isopropyl Alcohol:

Take 50.0kg of Isopropyl alcohol in SS vessel and slowly disperse Povidone K 90 in to it and stir well. Care should be taken while adding PVP K90 to avoid lump mass.

4. Granulation:

Add the binder solution slowly to the materials of dry mixing with impeller at slow speed and chopper off. Mix the wet mass for 1 minute with impeller slow and if require use chopper at slow speed. If require add extra quantity of Isopropyl alcohol with impeller at slow speed and impeller off NMT 1.5Kg of Isopropyl alcohol at a time within a period of 1-2 minutes. Every addition of Isopropyl alcohol mix for one minute,

impeller slow or high speed and adjust chopper speed slow or high to get the required granules size (20#).

5. Drying and Milling:

Load the wet granules into FBD and air dry the granules until no odour of isopropyl alcohol. Set the temperature as follow as for temperature drying.

Inlet temperature: 55 ± 5^0C

Outlet temperature: 40 ± 5^0C

Dry the wet granules till to reach LOD between 1.75 – 3.0 % at 105^0C. Perform the intermittent raking. Note the temperature for every 15 minutes. Sieve the dried granules through 20#. Mill the retained granules through multi mill fitted with 1.0 mm screen until pass through 20#. Whenever checking the LOD, note the outlet temperature.

6. Blending:

Load above dried granules and sifted materials of colloidal silicon dioxide into Double cone blender and allow mixing for 10 minutes at high speed.

7. Lubrication:

To the above blended granules add sifted batch quantity of sodium Stearyl fumarate to the above blend and mix for 5 minutes. Send the sample to QC for complete analysis bulk, tap density, particle size distribution and assay analysis.

8. Compression:

Upper punch: 14/32 (11.11mm) Circular shape, standard biconcave punch.

Lower punch: 14/32 (11.11mm) Circular shape, standard biconcave punch.

Compress the lubricated blend using above set punches and send the sample to QC for complete analysis as per current USP specification. After getting the QC report, start the compression and maintain the physical parameters within the specified limit.

7.4 Evaluation of Compressed Tablet

7.4.1 Description:

Blue coloured, Circular shaped, biconvex, film coated tablets having plain surface on both sides.

7.4.2 Weight Variation:

Weigh individually 20 tablets taken at random and determine the average weight. Not more than 2 of the individual weight deviate from the average weight. The percentage deviation shown in Table No.7.

Table No.7 Limits for Weight Variation

Average weight of tablet	Percentage deviation
80 mg or less	10
More than 80 mg but less than 250 mg	7.5
250 mg or more	5

7.4.3 Thickness:

It can be dimensionally described & controlled. Thickness may affect the hardness, disintegration time and dissolution rate. Tablet thickness can be measured by caliper for six tablets.

7.4.4 Diameter:

It also dimensionally described & controlled. Tablet diameter can be measured for six tablets by Dial calliper.

7.4.5 Friability:

It is expressed in percentage. Take a sample of whole tablets corresponding as near as possible to 6.5 gm. For tablets with a unit mass of more than 650 mg, take a sample of 10 whole tablets. The tablets are carefully dedusted prior to testing. Accurately weigh the tablet sample ($W_{initial}$) and place the tablets in the drum. Rotate

the drum 100 times at the rate of 25±2 rpm and remove the tablets. Remove any loose dust from the tablets as before, and accurately weigh (W_{final}).

$$\% F = \frac{(W_{initial}-W_{final})}{(W_{initial})} \times 100$$

7.4.6 Tablet Disintegration time:

Tablet disintegration study was performed only for immediate release tablet and for the immediate release layer of inlay tablet. Disintegration time was determined using USP tablet disintegration tester in distilled water.

7.4.7 Assay: (USP Monograph)

Determine the mean percentage value of the labelled amount of Metoprolol succinate from the tablets analysed in the test for Uniformity of Dosage Units.

Acceptance Criteria: 90.0mg to 110.0mg (90.0% to 110.0% of label claim)

7.4.8 Uniformity of Dosage Units: (USP Monograph)

Chromatographic Conditions:

Column	:	C_8 [4.0 mm X 12.5 cm, 5 µm] (L_7)
Flow rate	:	1.0ml/minute
Pump mode	:	Isocratic
Wavelength	:	280nm
Injection Volume	:	40 µL

Preparation of 1 M Monobasic sodium phosphate:

Weigh about 13.8 gm of monobasic sodium phosphate and transfer into 100 ml volumetric flask, dissolve and dilute up to the volume with water.

Preparation of 1 M Phosphoric acid:

Transfer 6.6 ml of phosphoric acid through pipette into 100 ml volumetric flask, dilute up to the volume with water.

Preparation of Buffer:

Mix 50 ml of 1 M monobasic sodium phosphate and 8.0 ml of 1 M phosphoric acid, dilute with water to 1000 ml. If, necessary adjust with 1M monobasic potassium phosphate or 1 M phosphoric acid to a pH of 3.0.

Mobile Phase:

Prepare a mixture of 250 volumes of Acetonitrile and 750 volumes of buffer solution. Mix and filter the solution through 0.45 µm nylon filter and sonication was done for 10 minutes.

Preparation of Standard Solution:

Weigh accurately 50 mg of Metoprolol succinate working standard and transfer into a 100 ml volumetric flask, add 50 ml of mobile phase and sonicate for 5 minutes to dissolve. Cool & dilute up to the volume with mobile phase. Transfer 5 ml of the above solution through pipette into a 50 ml volumetric flask & dilute up to the volume with mobile phase. Filter the solution through 0.45 µm nylon & collect the solution in an HPLC vial after discarding about first 2 ml of filtrate.

Preparation of Sample Solution:

Transfer one tablet into a 100 ml volumetric flask, add about 5 ml of water, and allow the tablet to disintegrate & add 30 ml alcohol & shake for 30 minutes. Add 50 ml of 0.1 N HCl to the flask, and shake for additional 30 minutes. Dilute up to the volume with 0.1 N HCl. Transfer 5 ml of the above solution into a 100 ml volumetric flask & dilute up to the volume with mobile phase. Filter the solution through 0.45 µm nylon & collect the solution in an HPLC vial after discarding about first 2 ml of filtrate.

Acceptance Criteria:

The acceptance value of the first 10 dosage units should be less than or equal to L1=15.0.

7.4.9 *In-vitro* Dissolution studies: (USP Monograph)

Dissolution Parameters:

Medium	:	pH 6.8 Phosphate buffer
Volume	:	500 ml
Apparatus	:	USP Type – II (Paddle)
Time	:	1^{st}, 4^{th}, 8^{th}, and 20^{th} hour.
Speed	:	50 RPM
Temperature	:	36.5^0C to 37.5^0C

Preparation of 0.2 M sodium hydroxide:

Weigh and dissolve 0.8 gm of sodium hydroxide in 100 ml of water.

Preparation of Dissolution medium:

Dissolve 6.8 gm of monobasic potassium phosphate and 0.9 gm of sodium hydroxide in 1000 ml of water. Adjust the pH to 6.80 ± 0.1 with 0.2 M sodium hydroxide.

Chromatographic Conditions:

Column	:	C_8 [4.0 mm X 12.5 cm, 5 µm] (L_7)
Flow rate	:	1.0ml/minute
Pump mode	:	Isocratic
Wavelength	:	280nm
Injection Volume	:	40 µL

Preparation of 1 M Monobasic sodium phosphate:

Weigh about 13.8 gm of monobasic sodium phosphate and transfer into 100 ml volumetric flask, dissolve and dilute up to the volume with water.

Preparation of 1 M Phosphoric acid:

Transfer 6.6 ml of phosphoric acid through pipette into 100 ml volumetric flask, dilute up to the volume with water.

Preparation of Buffer:

Mix 50 ml of 1 M monobasic sodium phosphate and 8.0 ml of 1 M phosphoric acid, dilute with water to 1000 ml. If, necessary adjust with 1M monobasic potassium phosphate or 1 M phosphoric acid to a pH of 3.0.

Mobile Phase:

Prepare a mixture of 250 volumes of Acetonitrile and 750 volumes of buffer solution. Mix and filter the solution through 0.45 µm nylon filter and sonication was done for 10 minutes.

Preparation of Standard Solution:

Weigh accurately 50 mg of Metoprolol succinate working standard and transfer into a 100 ml volumetric flask, add 50 ml of mobile phase and sonicate for 5 minutes to dissolve. Cool & dilute up to the volume with mobile phase. Transfer 5 ml of the above solution through pipette into a 50 ml volumetric flask & dilute up to the volume with mobile phase. Filter the solution through 0.45 µm nylon & collect the solution in an HPLC vial after discarding about first 2 ml of filtrate.

Preparation of Sample Solution:

Follow the dissolution parameters as mentioned in the above. After completion of specified different time intervals in dissolution test, collect 10.0 ml of sample solution in the middle of each dissolution jar & replace with 10.0 ml of dissolution medium after each withdrawal of the sample. Transfer 5 ml of the above solution through pipette into 20 ml volumetric flask & dilute up to the volume with dissolution medium. Filter the solution through 0.45 µm nylon & collect the solution in an HPLC vial after discarding about first 2 ml of filtrate.

Acceptance Criteria:

Time interval (hours)	Amount dissolved (%)
1st hour	Not more than 25 %
4th hour	20.0 % - 40.0 %
8th hour	40.0 % - 60.0 %
20th hour	Not less than 80.0 %

Data analysis:

The data obtained from the dissolution study were subjected for analysis to know the release pattern of the drug from the dosage form. To analyse the mechanism of release and release rate kinetics of the dosage form, the data obtained were fitted into Zero order, First order, Higuchi model and Korsmeyer-Peppas model. Based on the r-value, the best-fit model was selected.

Zero order kinetics:

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly, assuming that the area does not change and no equilibrium conditions are obtained can be represented by the following equation,

$$Q_t = Q_o + K_o t$$

Where Q_t = amount of drug dissolved in time t.

Q_o = initial amount of the drug in the solution

K_o = zero order release constant.

First order kinetics:

To study the first order release rate kinetics, the release rate data were fitted to the following equation,

$$\log Q_t = \log Q_o + K_1 t/2.303$$

Where Q_t is the amount of drug released in time t, Q_o is the initial amount of drug in the solution and K_1 is the first order release constant.

Higuchi model:

To study the Higuchi release kinetics, the release rate data were fitted to the following equation,

$$F = K.t_{1/2}$$

Where 'F' is the amount of drug release,' K' is the release rate constant and't' is the release time. When the data is plotted as a cumulative drug released versus square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'K'.

Korsmeyer – Peppas release model:

The release rate data were fitted to the following equation,

$$\frac{M\ t}{M\ \infty} = K.t^n$$

Where, M t / M ∞ is the fraction of drug release, 'K' is the release constant, 't' is the release time and 'n' is the diffusion exponent for the drug release that is dependent on the shape of the matrix dosage form. When the data is plotted as Log fraction of drug released versus Log time, yields a straight line with a slope equal to 'n' and the 'K' can be obtained from Y – intercept.

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45< n<0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n>0.89	Super case-II transport

i. Zero Order Reaction -% Cumulative drug release Vs Time in hrs
ii. First Order Reaction – Log % Cumulative drug remaining Vs Time in hrs
iii. Higuchi kinetics -% Cumulative drug release Vs square root of time
iv. Korsmeyer – Pappas equation -log cumulative % of drug released Vs log time

Blister Packing of Dosage form

Packing of dosage forms is important for reasons like

- Protection
- Identification
- Elegance
- Ease of Shipping

Blister packing is done for the selected formulation before being for the stability studies.

Packaging of Tablets:

Base foil and lidding foil were loaded in the machine. The tablets were loaded in the hopper. The base foil passes through the forming units with Teflon heads and cavities are formed. Tablets in the hopper coming down through inclined feeding channel and singling unit and are introduced into the cavities formed. The lidding foil introduced and the sealing of the foils was done in the sealing station. The non-filled cavities are detected using non fill detecting system and are rejected by non- filling detection rejection area. The cutting assembly and the trimming station cuts the blister into appropriate size.

STABILITY STUDIES

Introduction:

In any rational drug design or evaluation of dosage forms for drugs, the stability of the active component must be a major criterion in determining their acceptance or rejection. Stability of a drug can be defined as the time from the date of manufacture and the packaging of the formulation, until its chemical or biological activity is not less than a predetermined level of labelled potency and its physical characteristics have not changed appreciably or deleteriously.

Objective of the Study:

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of

environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives.

The International Conference on Harmonization (ICH) Guidelines titled "Stability Testing of New Drug Substance and Products" (QIA) describes the stability test requirements for drug registration applications in the European Union, Japan and the United States of America. ICH specifies the length of study and storage conditions. Accelerated Testing: $40^0C \pm 2^0C$/75 % RH ± 5 % RH for 6 Months.

Method:

Stability studies were carried out at 40^0C / 75 % RH for 6 months for the selected formulation. This formulation was selected because of its reproducibility of the *In-vitro* drug release of the drug from the extended release tablets. The formulation was charged for stability at conditions 40^0C / 75 % RH which are usually conditions for the Real time and Accelerated stability study. The formulation was tested for parameters like appearance, assay, uniformity of weight, *In-vitro* drug release.

Formulation	Stability Condition	Testing Frequency	Tested For
Selected Formulation	40^0C / 75 % RH	1^{st} month 2^{nd} month 3^{rd} month 6^{th} month	Appearance, Assay, Uniformity of weight, *In-vitro* drug release

RESULTS AND DISCUSSION

8. RESULTS AND DISCUSSION

Raw Material Analysis:

Solubility:

Metoprolol succinate was found to be freely soluble in water, soluble in methanol, sparingly soluble in ethanol, slightly soluble in dichloromethane and 2-propanol, insoluble in ethyl acetate, acetone diethyl ether and heptane.

Loss on Drying:

Loss on drying was determined and the results are illustrated.

Drug	Specification	Observation
Metoprolol succinate	Not more than 0.5%	0.2% ± 0.5334

The Loss on Drying for the drugs are within pharmacopoeial limits

Melting point of drug:

The melting point of Active ingredient was determined by capillary method.

Drug	Specification	Observation
Metoprolol succinate	120^0C	119.5^0C

PREFORMULATION STUDIES:

The overall objective of preformulation studies is to generate useful information to the formulator in developing stable and bioavailable dosage forms that can be mass produced.

Physical Drug-excipient Compatibility studies:

The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients that are added in the formulation. The drug and excipients must be compatible with one another to produce a product that is stable, Efficacious and easy to administer and safe.

The physical compatibility evaluation was performed in visual basis. The study implies that the drug, polymer and other excipients were physically compatible with each other as there was no change of physical description.

Drug and Drug – excipient Chemical Compatibility studies:

The samples that were charged in 45^0C/75% RH stability chambers were analysed by IR spectroscopy after 30 days. The graphs of the samples were given below:

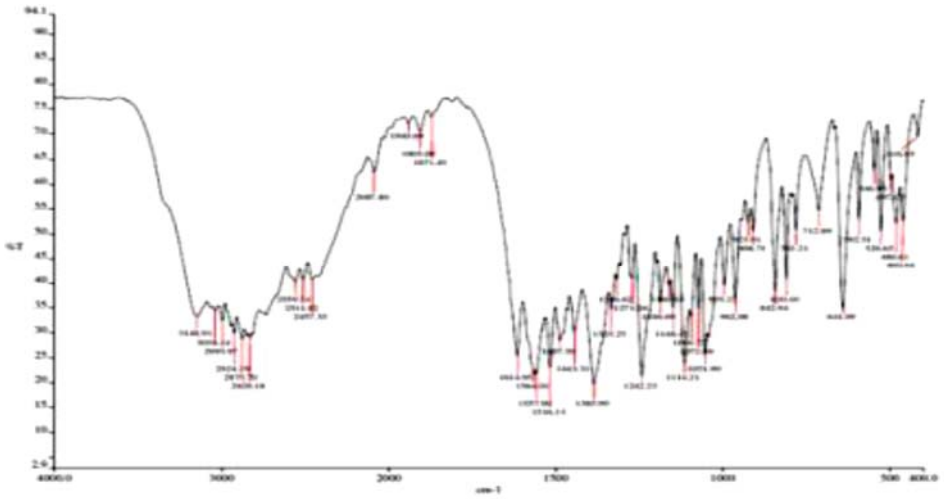


Figure 2 Infra-red spectra of pure drug Metoprolol succinate

Characteristic peaks of pure Metoprolol succinate

S.No	Type of bond	Type of vibration	Actual frequency (cm^{-1})	Observed frequency (cm^{-1})	Confirmation
1	C=C	Stretching	~ 1600	1614.95	Aromatic
2	N-H	Stretching	3310-3140	3148.91	2^0 amine
3	C-O	Stretching	1350-1260	1271.04	2^0 alcohol
4	C-O	Stretching	1150-1070	1148.45	Ether
5	C-O	Stretching	1410-1300	1385.99	Phenoxide

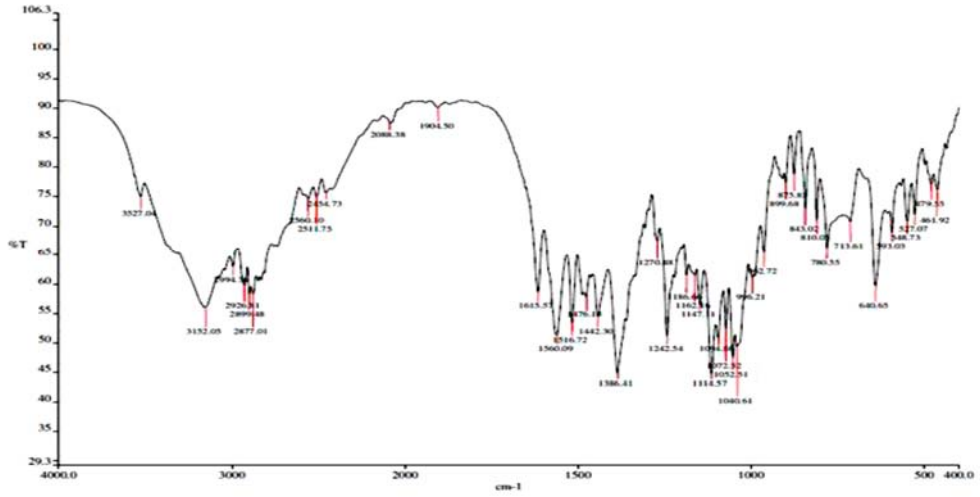


Figure 3 Infra-red spectra of Metoprolol succinate + HPMC K100M

Characteristic peaks of Metoprolol succinate in mixture of drug + HPMC K100M

S.No	Type of bond	Type of vibration	Actual frequency (cm^{-1})	Observed frequency (cm^{-1})	Confirmation
1	C=C	Stretching	~ 1600	1615.17	Aromatic
2	N-H	Stretching	3310-3140	3161.26	2^0 amine
3	C-O	Stretching	1350-1260	1271.08	2^0 alcohol
4	C-O	Stretching	1150-1070	1148.62	Ether
5	C-O	Stretching	1410-1300	1386.54	Phenoxide

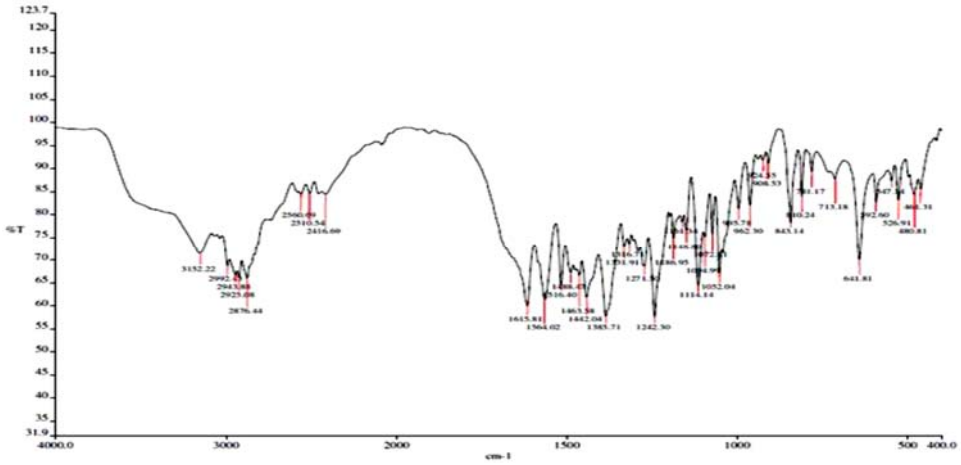


Figure 4 Infra-red spectra of Metoprolol succinate + HPMC K4M

Characteristic peaks of Metoprolol succinate in mixture of drug + HPMC K4M

S.No	Type of bond	Type of vibration	Actual frequency (cm^{-1})	Observed frequency (cm^{-1})	Confirmation
1	C=C	Stretching	~ 1600	1615.57	Aromatic
2	N-H	Stretching	3310-3140	3152.05	2^0 amine
3	C-O	Stretching	1350-1260	1270.48	2^0 alcohol
4	C-O	Stretching	1150-1070	1147.11	Ether
5	C-O	Stretching	1410-1300	1386.41	Phenoxide

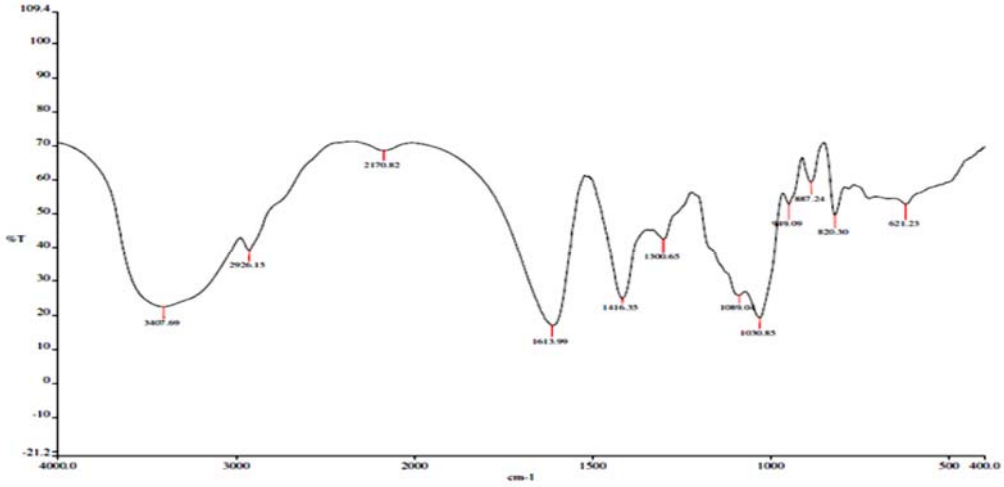


Figure 5 Infra-red spectra of Metoprolol succinate + HPMC K100M + HPMC K4M

Characteristic peaks of Metoprolol succinate in mixture of drug + HPMC K 100M + HPMC K 4M

S.No	Type of bond	Type of vibration	Actual frequency (cm^{-1})	Observed frequency (cm^{-1})	Confirmation
1	C=C	Stretching	~ 1600	1615.54	Aromatic
2	N-H	Stretching	3310-3140	3169.47	2^0 amine
3	C-O	Stretching	1350-1260	1271.00	2^0 alcohol
4	C-O	Stretching	1150-1070	1148.03	Ether
5	C-O	Stretching	1410-1300	1386.47	Phenoxide

Discussion:

From the IR studies and Physical observation it can be concluded that there will be no possible chemical interaction between the excipients and the drugs. So these excipients were used for the formulation.

There is no appearance or disappearance of any characteristic peaks. This shows that there is no interaction between the drug and polymer used.

Weight variation

The theoretical Average weight of the various formulated tablets are 475mg and weight variation of the various formulation are depicted in the Table No.8. The percentage deviation of the weight was within 5% as per monograph.

Hardness

The hardness of the various tablet formulation was shown in Table No.8. The hardness tablet found in the ranges from 5.91 to 6.8. So, it was the sufficient hardness for tablet, coating, transporting, and packing.

Table No.8 Physical Parameters of Extended Release Tablets

Formulation	Weight variation**	Hardness*	Thickness*	Friability*	Diameter*	Drug content*
F_1	470.5±19.59	6.08±0.491	6.48±0.113	0.200±.102	13.11±0.006	101.23±0.05
F_2	473.3±7.97	5.91±0.376	6.42±0.214	0.176±0.071	13.10±0.007	101.53±0.06
F_3	465.3±6.76	6.66±0.516	6.61±0.063	0.245±0.176	13.10±0.005	102.04±0.01
F_4	472.4±10.9	6.41±0.204	6.63±0.017	0.103±0.045	13.11±0.004	103.21±0.04
F_5	470.0±1.63	6.33±0.258	6.62±0.082	0.107±0.025	13.10±0.008	99.71±0.04
F_6	472.1 ±1.72	6.41±0.204	6.52±0.129	0.113±0.019	13.10±0.005	99.43±0.04
F_7	474.5±0.59	6.25±0.273	6.50±0.064	0.123±0.014	13.10±0.006	101.38±0.01

Thickness

The thickness of the various tablet formulation was shown in the above Table No.8. The thickness of the tablet found in the ranges from 6.42 to 6.63. It was important for packing of tablet and acceptance.

Friability

The friability of the various tablet formulation was shown in the above Table No.8. The friability of the tablet found in the ranges from 0.1 to 0.2. The values are within limit of the official monograph.

Diameter

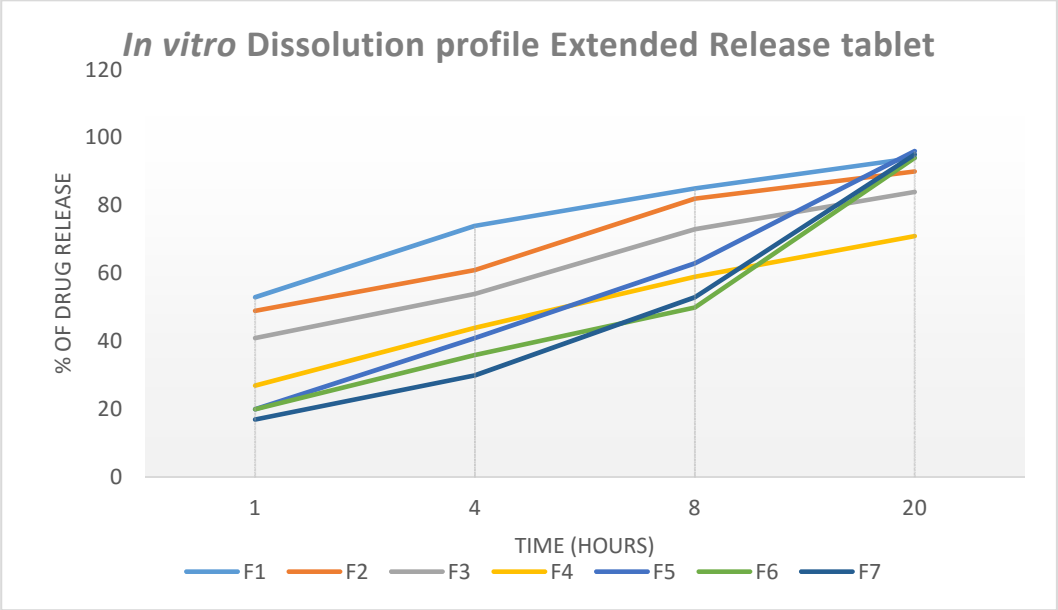
The diameter of the tablet found in the ranges from 13.1 to 13.11. It was important for packing of tablet and acceptance. The diameter of the various tablet formulation was shown in the above Table No.8.

Drug content

The content of the various formulation was analyzed by High Performance Liquid Chromatography method. It was very important for the release percentage from the amount present in the tablet. The percentage of drug fount in the ranges from 99.43 to 103.21. The drug content of various formulation was shown in the above Table No.8.

Table No.9 ***In vitro Dissolution profile Extended Release tablet***

Time in hrs	1	4	8	20
F_1	52.92±1.367	73.73±1.108	85.25±1.222	94.05±0.799
F_2	48.95±0.399	61.21±0.385	82.16±0.887	90.71±1.391
F_3	40.54±1.41	53.71±0.804	72.55±1.188	83.66±0.989
F_4	26.75±0.947	43.78±0.817	58.64±1.515	71.36±0.904
F_5	20.17±0.782	40.99±0.572	62.56±0.718	95.52±0.56
F_6	19.87±0.862	35.60±0.439	49.98±1.002	94.12±0.51
F_7	16.73±0.685	30.38±1.391	52.80±0.3416	94.35±1.456



In vitro dissolution release profile of various formulation studied. From the results of *in vitro* Dissolution studies of Extended Release formulations it was observed that the formulation F_1 to F_7. Formulation F_4 having a release profile up to 12 hours was selected for formulation of ER tablet. It was concluded that the drug release from the hydrophilic polymer HPMC $_{K100M}$ shows the better release rate. The concentration of polymers respect to the drug was 40%w/w. So, the polymer concentration increase the release time also increases. All the polymer showed the sustained release property.

Drug release comparison of optimized batch with pure drug sample (API):

Chromatogram study:

The optimized batch of formulation drug release was gradually increases with time (fig 7, 8, 9, 10) at 1st, 4th, 8th, 20th hour. The 20th hour chromatogram of the optimized formulation (F7) was MATCH with the chromatogram of the pure drug sample (API) at 0 hour (fig 6).

Fig 6 Dissolution Standard Chromatogram

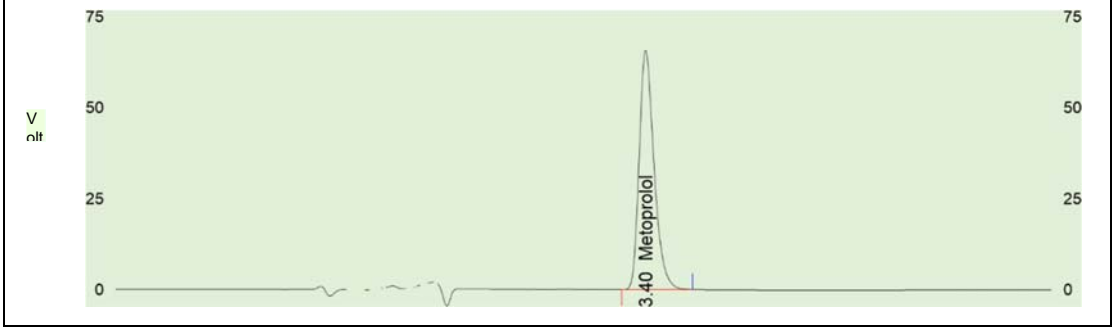


Fig 7 Dissolution Test for 1st Hour

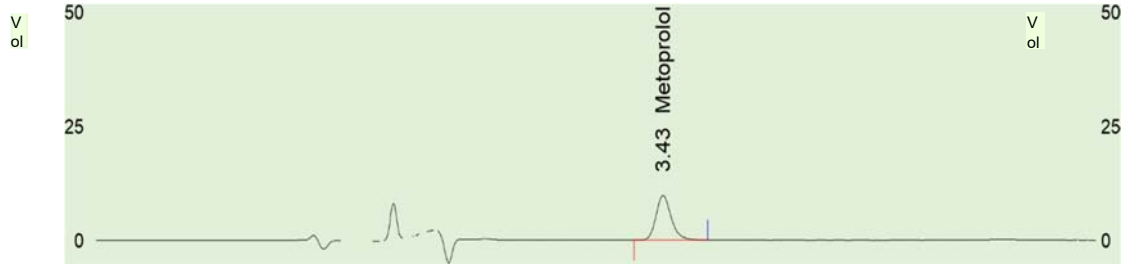


Fig 8 Dissolution Test for 4th Hour

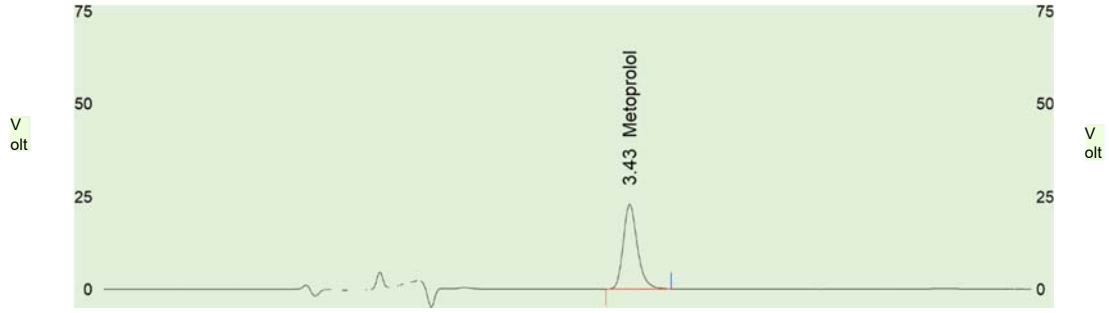


Fig 9 Dissolution Test for 8th Hour

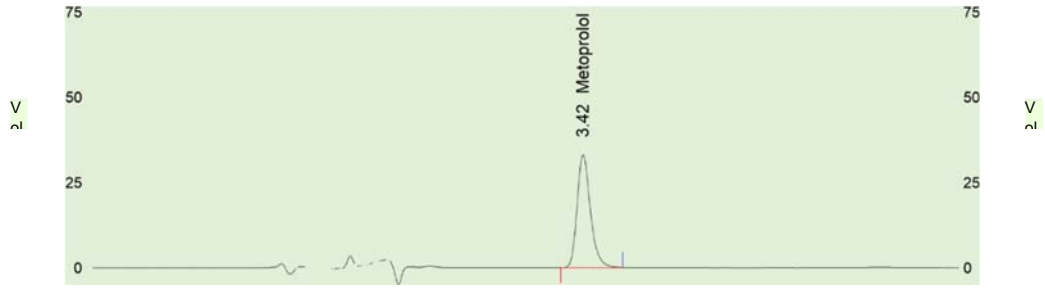


Fig 10 Dissolution Test for 20th Hour

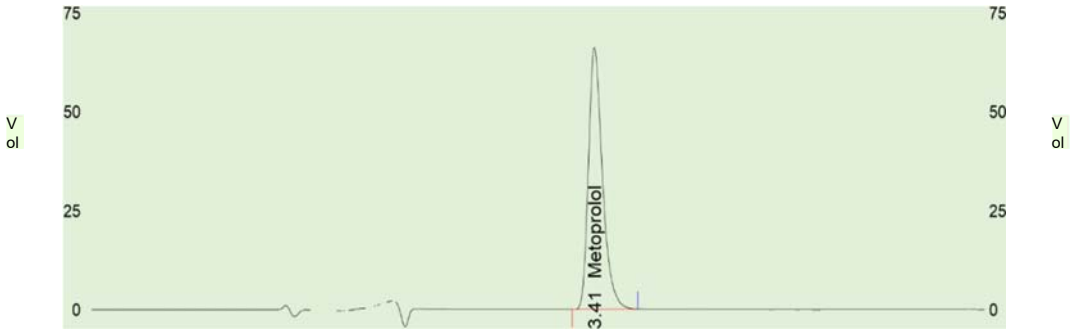


Fig 11 Standard Chromatogram for Uniformity of Content

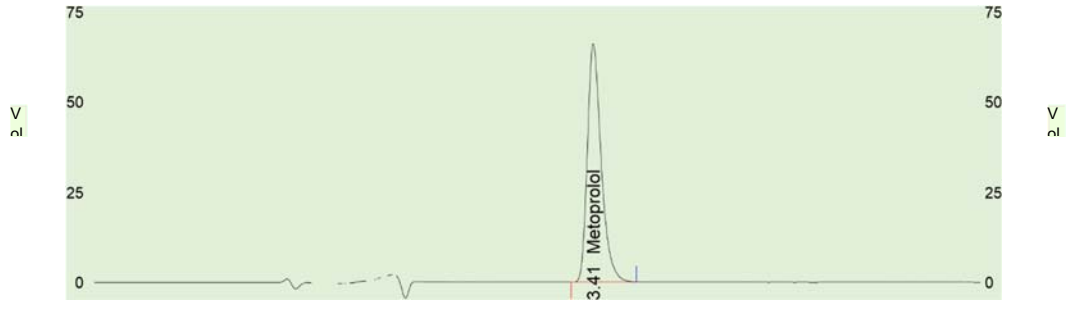
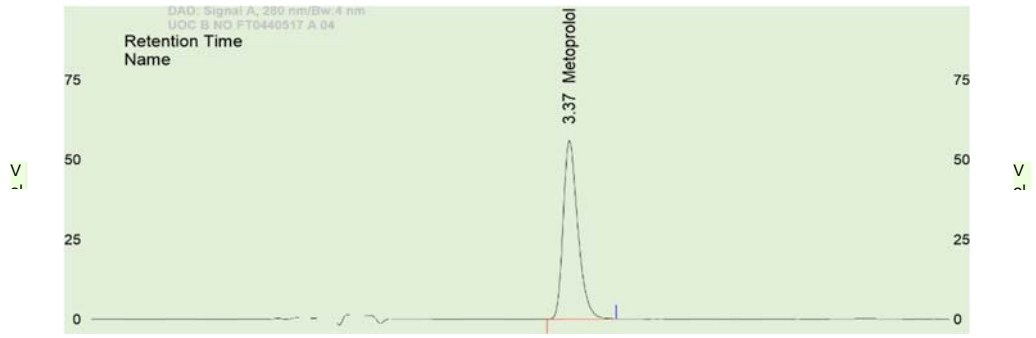


Fig 12 Sample Chromatogram for Uniformity of Content



Kinetic Study:

Formulation – 7 was found to be giving the desired *in vitro* dissolution rate, so this formulation was selected for determining the nature of release of drug from dosage form.

Formulation	Zero-order kinetics		First-order kinetics		Higuchi's kinetics		Korsmeyer-Peppas	
Formulation - 7	Slope	R^2	Slope	R^2	Slope	R^2	Slope	R^2
	8.425	0.786	0.227	0.996	31.65	0.964	-0.406	0.954

The curve fitting results of the release rate profile of the designed formulations gave an idea on the mechanism of drug release. Based on the data analysis the drug release was found to follow First order kinetics, the drug release mechanism was best explained by first order, as the plots showed the highest linearity. This model indicates a coupling of the diffusion and erosion mechanism (Anomalous diffusion) and indicates that the drug release was controlled by more than one process.

Stability Study Data:

The samples from the stability chambers that were packed in PVC Blister packing were subjected to following analysis.

Parameter	Specifications		Initial	1st month at 40^{0}C/ 75% RH
Appearance	Blue colour, Circular shaped, biconvex film coated tablets having plain surface on both sides.		Complies	Complies
Average weight of 20 tablets	475.00mg ± 3.0%		477.86mg	476.34mg
Weight variation	±3.0%		-0.59% to + 0.50%	-1.02% to +1.20%
Assay: Each film coated tablet contains, 95mg Metoprolol Succinate USP is equivalent to 100mg of Metoprolol Tartrate USP	90.00 % to 110.00 % of label claim (85.50mg to 104.50mg of Metoprolol Succinate)		100.64% of label claim (95.82mg of Metoprolol Succinate)	100.03% of label claim (95.01mg of Metoprolol Succinate)
In-Vitro drug release profile	1st hour	NMT 25.00%	16.73%	16.06%
	4th hour	20.00% to 40.00%	30.38%	30.42%
	8th hour	40.00% to 60.00%	52.80%	53.14%
	20th hour	NLT 80.00%	94.35%	95.42%

SUMMARY AND CONCLUSION

9. SUMMARY AND CONCLUSION

The Present research endeavour is directed towards the development of **once daily extended release matrix Tablet of Metoprolol succinate equivalent to Metoprolol Tartrate 100mg.**

The different concentration of polymer was used to control the drug release from the dosage form (USP Monograph limits).

This extended release tablet is effective in improving the hypertension control by blocking the beta2 adrenergic receptors. Matrix System was based on swellable polymer were selected for sustaining the drug release. Different polymers to get the desired release profile over a period for 20 hours. Different batches of extended release was prepared by Wet granulation Method respectively.

All the formulations were evaluated for physical characteristics, disintegration, in vitro dissolution study and stability. Following conclusions have been made from the present study.

- The **physical characteristics** of all the blended formulations were satisfactory.
- The prepared tablets evaluated for **Assay, weight variation, hardness, thickness and friability and Disintegration time** were found to be within the official limits.
- The ***in vitro*** **dissolution studies** were performed for all the **ER formulations.**
- ***In Vitro*** **Dissolution study of ER formulations F_7** showed release profile were complies with USP at 40% concentration of $HPMCK_{100M}$ with respect to drug compared with another 6 formulation.
- *In-vitro* Dissolution study of ER Tablets was compared to the API.

REFERENCES

10. REFERENCES

1. Remington, The Science and pharmacy practice of Pharmacy, 21st edition volume I, II, 869870.
2. Kewel K Jain, Drug delivery system, Third Edition, 217-219.
3. Lachman, L., Liberman, H.A., and Kanig, J.L. The Theory Practice of Industrial Pharmacy. Lea Febiger, Philadelphia. 293-294,226-328.
4. Hebert A. Liberman. Leon Lachman, Joseph B. Schwartz. Pharmaceutical dosage forms tablet- Vol-1, Vol-2, 112.220.
5. Anisul Quardir, Karl Kolter, A comparative study of current Super disintegrants, pharmaceutical technology, Oct 1, 2006.
6. Leon Lachman, Joseph B.Schwartz, compression coated and layered Tablets, Pharmaceutical Dosage forms: Tablets, 1989, Vol II, 273-274.
7. R.S.Sathoskar, S.D, Bhandarkar, Nimala N.Rege, Pharmacology and pharmacotherapeutics, Ninth edition,884-891.
8. Gilbert S. Banker, Christopher T. Rhodes, Modern Pharmaceutics, 4th Edition, 121, 2005, Marcel Dekker, Inc, 501-514.
9. Thomas Wait-Yip Lee and Joseph R Robinson, Controlled Release Drug Delivery system, In the Science and Practice of Pharmacy, Volume 1, 20th edition, 2001, 903.
10. Yie W. Chein, Oral Drug Delivery System, Novel drug delivery Systems, volume 50, 2nd Edition, Marcel Dekker, Inc., 139-157.
11. Donald L. Wise, Hand Book of Pharmaceutical Controlled Release Technology, 2005, Marcel Dekker, Inc, 435-440.
12. Gwen M. Jantzen and Joseph R. Robinson, Sustained and controlled Release Drug Delivery System, In Modern Pharmaceutics, Marcel Dekker, Inc., 3rd edition, 1996, 582-593.
13. Li VHK, Robinson JR, Lee VHL, Design and Fabrication of oral Controlled Drug Delivery System, In Controlled Drug Delivery, Marcel Dekkar 1987, 2nd edition, 412.

14. Agis Kydonieus, Treatise on Controlled Drug Delivery, Marcel Dekker 1st Edition, 1992, 43-93.
15. S.P. Vyas, Roop. K. Khar, Controlled Drug Delivery Concept and Advances, 1st edition, 2002, 54-71.
16. British Pharmacopoeia. The Stationary office, MHRA, British Pharmacopoeial Commission office, Vol. 1, London, 2004.
17. Raymond C Rowe, Paul J Sheskey and Sian C Owen, Hand Book Of Pharmaceutical Excipients, 5th edition, 2006, 553-560.
18. Raymond C Rowe, Paul J Sheskey and Sian C Owen, Hand Book Of Pharmaceutical Excipients, 5th edition, 2006, 278-282.
19. P. Lundborg *et al*. Pharmacokinetics and pharmacodynamics of metoprolol after conventional and controlled-release administration in combination with hydrochlorothiazide in healthy volunteers, European Journal of Clinical Pharmacology, 45(2)1993, 161-163.
20. Hema Ravishankar *et al*. Modulated release metoprolol succinate formulation based on ionic interactions: In vivo proof of concept, Journal of Controlled Release, Volume 111, Issues 1-2, 2006, 65-72.
21. James W Hainer *et al*. Metoprolol succinate extended release/hydrochlorothiazide combination tablets, Am J Hypertens.19 (12), 2003, 117-25.
22. Papademetriou V. Factorial antihypertensive study of an extended-release metoprolol and hydrochlorothiazide combination, Am J Hypertens.19 (12), 2006, 1217-25.
23. Papadopoulos DP *et al*. Metoprolol succinate combination in the treatment of hypertension. Angiology. 60(5), 2009, 608-13.
24. Plosker GL *et al*. Controlled release metoprolol formulations. A review of their pharmacodynamics and pharmacokinetic properties, and therapeutic use in hypertension and ischaemic heart disease, Drugs. 1999; 43(3):382-414.
25. Nagaraju *et al*. Core-in-Cup Tablet Design of Metoprolol Succinate and its Evaluation for Controlled Release, Current Drug Discovery Technologies, Volume 6, Number 4, 2009 , 299-305.

26. Tilak R. Bhardwaj *et al*. Natural Gums and Modified Natural Gums as Sustained-Release Carriers, Drug Development and Industrial Pharmacy, Vol. 26, No. 10, 2000, 1025-1038.
27. F. Siepmann *et al*. Polymer blends for controlled release coatings, Indian Journal of Pharmaceutical Sciences, 61(6), 1996, 42-5.
28. Udaya S. Toti et al., Modified guar gum matrix tablet for controlled release of diltiazem hydrochloride, Indian Journal of Pharmaceutical Sciences, 61(6), 1998, 212-5.
29. Khullar P et al., Guar Gum as a hydrophilic matrix for preparation of Theophylline Controlled Release dosage form, Indian Journal of Pharmaceutical Sciences, 61(6), 1999, and 342-5.
30. Praveen Khullar *et al*. Evaluation of Guar Gum in the Preparation of Sustained-Release Matrix Tablets,1998, Vol. 24, No. 11, 1998, 1095-1099.
31. James W Hainer and Jennifer Sugg; *Vascular Health and Risk management*, **2007**, 3(3), 279–288.
32. Yie Chein; Novel drug delivery system" 2nd. Marcel jekkerinc. New York. **1992**, 1-3.
33. VH Lee and JP Robinson, sustained and controlled release drug delivery system". Marceldekker, New York, **1978**, 7-11.
34. S Vidyadhara; P R Raoand J A Prasad, *Indian J. Pharm. Sci.,* **2004**, 66, 188-192.
35. Vishnu.M.Patel, HarshaV.patel, Bhupendra and Prajipatil. *AAPS Pharm SciTech.*, **2007**, 77, E1-E6.
36. J Cooper and C Gunn; Powder flow and compaction. In: Carter S.J, Tutorial Pharmacy, CBS publishers, New Delhi, **1986**, 211–233.
37. JS Remington and G Desmonts; Toxoplasmosis. In: Remington, J.S. & Klein, J.O. (eds)Infectious diseases of the fetus and new-born infant, WB Saunders Company,Philadelphia, **1990**, 89-195.
38. L Lachman; H Lieberman and J Kanig, The theory and practice of industrial pharmacy. Varghese publication house, 3rd edition, **1987**, 299.
39. YR Sharma; Elementary Organic Spectroscopy Principles and Chemical Applications.S .Chand & Co, **1991**, 296- 302.

40. P Koteswararao; S Duraivel; KP Sampath Kumar and Debjit Bhowmik, *Indian Journal of Research in Pharmacy and Biotechnology,* **2013**, 1(5), 629-634.
41. NavneetVerma and PronobeshChattopadhyay, *Asian Journal of Pharmaceutical and Clinical Research,* **2012**, 5(1), 168-171.
42. M Mohamed Raffick; J Muthu Mohamed; S Vetriselvan; M Vignesh; K Selvakumar;V Parkavi and J JoysaRuby, *International Journal of Biological & Pharmaceutical Research,* **2012**; 3(2): 284-296.
43. AR Mullaicharam; PM Shumo and P Muthuprasanna, *International Journal of Pharma Biosciences*, **2010**, 1(2), 1-10.